BIO-OLEFINS PREPARED BY ACYCLIC DIENE METATHESIS

By

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by

Timothy Edward Hopkins

This document is dedicated to my loving and supportive parents Ed and Patricia Hopkins. Also, I would like to add a special dedication to my friend Bob Christie, a true friend who was always there to listen and cheer me up during the bad times and to join me in celebration during the good times. Bob, I will always miss you.

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Abstract of Dissertation Presented to the Graduate School
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BIO-OLEFINS PREPARED BY ACYCLIC DIENE METATHESIS

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The incorporation of amino acids and peptides into polymers can result in materials with desirable properties, such as enhanced solubility, secondary structure formation, biodegradability, and/or biocompatibility. Amino acid/peptides can be incorporated into a polymer via two methodologies. The first entails the incorporation of the amino acid/peptides directly into the backbone of a polymer resulting in a poly(ester amide), which should be biodegradable. The other main method of incorporation is to branch amino acids/peptides off of the polymer backbone, resulting in a polymer with a backbone that is not biodegradable and not soluble resulting in a material with the potential use for biologically active surfaces.

Acyclic diene metathesis (ADMET) has been used to prepare poly(ester amide)s containing an amino alcohol moiety. It was found that the proximity of the functionality to the olefin was important: the polymerization suffers from slow kinetics when the functionality is located three or less carbons from the olefin. In addition, the polymers are semicrystalline, and demonstrate an increased melt upon hydrogenation.

The branched amino acids/peptides can be attached to the diene through either the *C* or *N*-terminus yielding monomers with different reactivities. Polymers with an amino acid on every 9th carbon polymerize when attached through the *N*-terminus but not through the *C*-terminus, and this trend is continued for the highly polar arginine branched monomer located at every 21st carbon. Also, the solvent used played a profound role on the polymerizability, where THF was determined to be the ideal solvent for the polymerization of these highly polar monomers.

In addition, these amino acid/peptide containing polyolefins, termed bio-olefins, have interesting physical properties. Over half of the polymers prepared are semicrystalline with T_ms up to 150 °C and up to 60 % crystallinity as determined by DSC and WAXD, respectively. Initial Instron testing demonstrates that bio-olefins have good material properties, *i.e.* elasticity and high tensile strength, probably due to the high degree of functionality and hydrogen-bonding ability. Further, surface studies demonstrate that the functionality is located on the surface at 45° and 90° for nonbulky and bulky peptides, respectively.

CHAPTER 1
BACKGROUND ON CHIRAL POLYOLEFINS

Introduction

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For the purpose of this chapter "chiral polyolefins" are defined as any polymer with a hydrocarbon backbone that demonstrates optical activity or can be resolved into an optically active entity. Thus, chiral polyolefins consist of two major classes of polymers. In the first class, the chirality is introduced because of tacticity formed during the polymerization; and the second involves the attachment of chiral compounds to monomers — usually vinyl monomers. The field of chiral polyolefins, which dates to the 1950's, continues to be a subject of much interest.[1,2] Applications of chiral polyolefins range from chiral recognition polymers for use as stationary phases to new biomimetic polymers that imitate nature's chiral polymers, peptides, and DNA.[3,4]

Chiral polyolefins formed due to tacticity have become important in the field of chiral recognition because of their tendency to form helices. These polymers consist primarily of a class of vinyl polymers with bulky substituents. For example, triphenylmethyl methacrylate can be polymerized with a chiral anionic initiator to yield an optically active polymer that forms a one-handed helix; the polymer has chiral recognition ability and can serve as a stationary phase in HPLC to separate racemic compounds.[3]

The second class consists of polymers synthesized from chiral vinyl monomers, chiral vinyl ethers, chiral vinyl ketones, chiral acrylamides, and chiral acrylates. In the 1960s and 1970s, much work was done with these polymers to study the effect of chirality on the sterespecificity of polymerizations, and to study the specific rotation of the resulting optically active polymers.[1] In the early 1990s, chiral polyolefins were of interest for studying the impact of chiral spacers between the vinyl group of the monomer and an achiral chromophore to create polymers that have helical structures. These helical structures can lead to nematic or smectic liquid crystalline phases, which can lead to polymers with interesting optical and electronic properties.[5-7]

Amino acid-branched polymers have been the topic of much interest due to their potential use as biocompatible materials. The use of amino acids to synthesize chiral polymers dates back to the 1960s; however, the expense of the amino acids limited the amount of research performed.[8] Recent advances in the areas of purification and synthesis of amino acids have made them more available, increasing the amount of research in which amino acids are used to create chiral polymers.[4] Amino acid-containing polymers have hydrogen-bonding abilities that can lead to higher-ordered structures such as α-helices and β-sheets. Possible uses of amino acid branched polyolefins include biomaterials, drug-delivery agents, chiral recognition stationary phases, asymmetric catalysts, and metal ion absorbents.[4]

This chapter highlights work in the area of chiral polyolefins. The emphasis is on the synthesis, properties, and possible uses of chiral polyolefins. Specifically, the focus is primarily on chiral polyolefins synthesized from chiral vinyl monomers, chiral polymers from achiral vinyl monomers, chiral vinyl monomers with aromatic substituents, and chiral vinyl monomers attached to amino acids.

Hydrocarbon-Based Chiral Polyolefins

Chiral Vinyl Hydrocarbon Polymers

The study of chiral vinyl monomers originated from the discovery by Natta *et al.* [9] that the polymerization of racemic 4-methyl-1-hexene (**1b**) with Ziegler-Natta catalyst systems yielded highly crystalline isotactic polymers melting at 188 °C (Figure 1-1). This was opposite of the findings for straight chain branches, such as the isotactic polymerization of 1-hexene, which has a melt transition below room temperature.[10] Two explanations were given for the unexpected high crystallinity of the racemic polymer: the hydrocarbon branch did not affect the crystalline lattice, and the individual polymer was composed of only one enantiomer.[11] Much research was performed in the 1960s and 1970s to determine the reasons for the high degree of crystallinity.

Bailey and Yates investigated the polymerization of (*S*)-3-methyl-1-pentene (**1a**) using the Ziegler-Natta catalyst systems ($Al(iBu)_3$, $TiCl_4$).[10] There were two isolatable fractions: a partially crystalline xylene insoluble fraction with a specific rotation of +94.9°, and a highly crystalline xylene soluble fraction with a specific rotation of -257°. The first polymer was believed to be atactic, whereas the latter was believed to be isotactic with a predominance of one enantiomer in the main chain.[10]

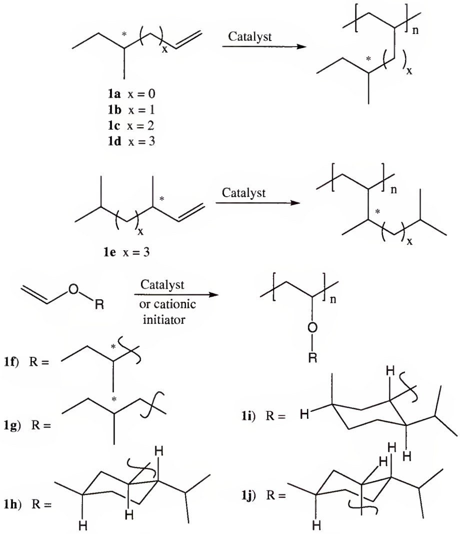


Figure 1-1. Chiral vinyl hydrocarbon polymers and chiral vinyl ether hydrocarbon polymers.

Further research in this area by Pino *et al.*[12] involved the polymerization of (*S*)-3-methyl-1-pentene (**1a**), (*S*)-4-methyl-1-hexene (**1b**), and (*S*)-5-methyl-1-heptene (**1c**). Optical rotations 5 to 28 times larger than model compounds (paraffins) of similar structure were found for all three. The difference in optical rotation of the polymer to small molecule was compared to that of spirilized proteins, which led to the conclusion that the isotactic polymers formed a 1-handed helix type of secondary structure. The helix confirmation was later supported when Pino and coworkers successfully resolved polymers of racemic 4-methyl-1-hexene into optically active polymers, and further confirmed by circular dichroism.[13,14] Since the polymer of the racemic monomer could be resolved, it was suggested that each chain consisted of primarily one enantiomer.

Placement of the chiral center with respect to the alkene had a large impact on crystallinity and optical rotation. For example, poly-(*S*)-5-methyl-1-heptene (**1c**) and poly-(*S*)-6-methyl-1-octene (**1d**) have much lower optical rotations than those observed for polymers having a chiral center in the α (**1a**) or β (**1b**) positions.[15] Therefore, polymers having a chiral center farther than one carbon away from the backbone have less stereoregularity — very low isotacticity — and lower optical activity.[15-17] This was due to the presence of syndiotactic and atactic run lengths, which could prevent helical conformation.[15]

Stereoselective polymerization and stereoelective polymerizations were also investigated. The first term means that the polymerization of a racemic mixture results in a polymer containing a predominance of one *R* or *S* monomeric unit; and the latter term relates to a polymerization where one of the monomeric enantiomers is preferentially polymerized.[11] Stereoselective polymerizations result in a polymer that can be resolved into optically active fractions, whereas the stereoelective polymerizations yield an optically active polymer as well as optically active unreacted monomer. In an effort to stereoelectively polymerize one enantiomer of a racemic mixture, the asymmetric catalyst $TiCl_4$ and bis[(*S*)-2-methylbutyl]zinc was used to polymerize 3,7-dimethyl-1-octene (**1e**) and 3-methyl-1-pentene(**1a**). The *S* enantiomer was predominately polymerized; however, only optical rotations of 13 - 14° were found, which is much less than that found for the polymer of the pure enantiomer.[18]

The chiral center location and the chiral catalyst chosen greatly affect the success of the stereoelective polymerization. Only monomers with chirality located at the α position were capable of stereoelective polymerization, and ZnR_2 —* not AlR_3* or BeR_2* — successfully catalyzed the stereoelective polymerization.[11] Copolymerization of (*S*)-3-methyl-1-pentene (**1a**) with racemic 3,7-dimethyl-1-octene (**1e**) resulted in a stereoelective polymerization of the racemic comonomer; the pure *S* monomer causes preferential polymerization of the *S* comonomer of the racemic compound, as verified by the recovery of unreacted *R* comonomer.[17] Ciardelli *et al.* found that the $TiCl_4$/ Zn(*i*-$C_4H_9)_2$ stereoelectively polymerized monomers with chirality in the α position, but was only slightly stereoelective for monomers with chirality in the β position, and not stereoelective when the chirality was in the γ position.[19] The optical rotation of the polymer and the optical purity of the monomer did not vary linearly, demonstrating that the stereoselectivity of the polymerization was not complete and that this was not due to a variance in stereoregularity. The tacticity and optical activity were maximized by the use of monomers with greater than 50-70 % enantiomer purity.[19]

Recently, syndiotactic poly-(*S*)-4-methyl-1-hexene (**1b**) was prepared using new metallocene catalysts.[20-22] The polymers generated an increase in optical activity similar to the isotactic polymers mentioned earlier, demonstrating that the optical purity of the side chains, the position of the chirality in the monomer, and the stereoregularity of the polymer — isotactic or syndiotactic — determined the ability of the polymer to form highly ordered structures.

Chiral Vinyl Ether Polymers with Hydrocarbon Chirality

Other research by Pino *et al.*[23-26] demonstrated that the chiral vinyl ether polymer poly[(*S*)-1-methyl propyl] vinyl ether (**1f**) with chirality located at the β position shows the same optical activity increase as the chiral vinyl hydrocarbon polymer (**1b**) with chirality at the β position (Figure 1-1). However, when the optical activity was in the γ position with respect to the alkene as in poly[(*S*)-2-methyl butyl] vinyl ether (**1g**), the vinyl ether polymer had a much lower optical activity than the corresponding vinyl hydrocarbon polymer (**1c**). They concluded that the ether linkage gave increased mobility to the side chain, resulting in the inability of the chiral center to induce stereoregularity into the polymer.[27] Stereoregularity played the biggest role in whether there was an increase in optical activity and thus formation of a secondary structure.[26] Further, the polymerization of racemic vinyl ethers with chirality in the γ position was not stereoselective, even if the polymer was isotactic, as was evident by the inability to resolve the polymers into optically active fractions.[28]

The synthesis of chiral vinyl ethers bearing multiple chiral centers has been performed by polymerizing (-)-Menthyl vinyl ether (**1h**) with 1:9-Ni-MoO_3 and 1:9-Mn-MoO_3 catalysts.[29,30] The polymers had an optical activity three times higher than the monomers, which was attributed to the additional conformational rigidity of the polymer compared to the monomer. (+)-Isomenthyl vinyl ether (**1i**) and (+)-neomenthyl vinyl ether (**1j**) were also polymerized.[31] The optical rotations of these polymers were similar to that of the monomer for (+)-isomenthyl vinyl ether (**1i**) and much greater than the monomer for (+)-neomenthyl vinyl ether (**1j**). Model compounds demonstrated that poly-(+)-isomenthyl vinyl ether (**1i**), unlike the other two polymers, did not show any preference for isotactic polymerization. However, explaining this lack of stereoregularity is difficult, because the branch contains three chiral centers.[31]

Chiral Vinyl Ketone, Acetamide, and Acrylate Polymers with Hydrocarbon Chirality

Chiral vinyl ketones containing hydrocarbon chirality have been synthesized both anionically and radically (Figure 1-2).[32-34] Anionic polymerization of these molecules can give isotactic structures, whereas the radical polymerizations yield atactic polymer. A similar increase in optical activity was observed for the isotactic poly(vinyl ketones) as was seen for the chiral vinyl ethers. Increases in optical activity were only significant when the chirality was located on the β-carbon relative to the vinyl group (**2a**), due to the influence of the chirality on the propagating species.

Chiral poly(acrylamides)[35-37] and poly(acrylates)[38-41] have been polymerized by both anionic and radical methods. Most of the polymers, even if they are stereoregular, do not show appreciable increases in optical activity, since the chirality is too far removed from the main chain of the polymer. Many chiral poly(acrylamides) and poly(acrylates) have been prepared, due to the ease of coupling of chiral amines and chiral alcohols to acrylic acid and methacrylic acid. For example, Arlt *et al.*[37] synthesized poly(methacrylamides) bearing menthol derivatives, which are connected to the vinyl group by an amino acid moiety (**2b**), and the polymers show the ability to separate racemic compounds. Uno *et al.*[42] and Lee *et al.*[43] have prepared poly(methacrylates) bearing menthol (**2c**) and cholesterol (**2d**) derivatives respectively. The polymers prepared by Uno *et al.*[42] (**2c**) that were highly isotactic had a large decrease in optical activity compared to the atactic polymers, which was attributed to secondary structure formation. The polymers bearing cholesterol derivatives (**2d**) were atactic and did not show a significant increase in optical activity, but the optical activities did change depending on the temperature, a property of polymers with chiral confirmations.[43] Examples of poly(acrylates) and poly(methacrylates) in uses as liquid crystalline polymers and biopolymers are discussed separately in this chapter.

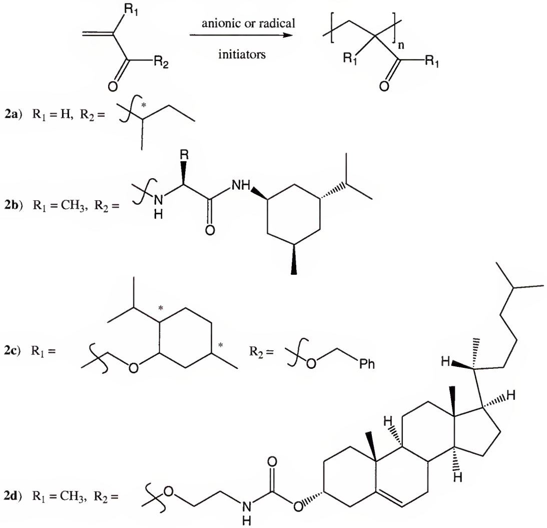


Figure 1-2. Chiral vinyl ketones, acrylates, and acrylamides.

Chiral Polyolefins from Achiral Monomers

Chiral polyolefins prepared from achiral monomers have been synthesized by polymerizing methacrylates, acrylamides, and methacrylamides with bulky substituents in the 1 position of the alkene (Figure 1-3).[3] This type of chiral polyolefins has been discussed in detail in recent reviews, so the topic is discussed only briefly in this chapter.[3,44] Triphenylmethyl methacrylate (TrMA) (**3a**) can be polymerized by radical or anionic methods to give an isotactic polymer.[45,46] Although the monomer contains no chirality, the bulky side group leads to an isotactic polymer that forms left and right handed helices. Polymers exhibiting high optical activity have been synthesized using chiral initiators.[47-54] Okamoto and coworkers found that the resulting optically active polymers have high chiral recognition ability, especially when the racemates possess aromatic rings.[55,56]

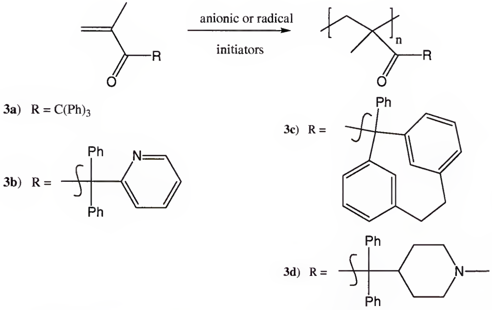


Figure 1-3. Chiral polyolefins from achiral monomers.

The successful chiral recognition ability of poly(TrMa) (**3a**) has led to the polymerization of a variety of bulky acrylates and acrylamides, as well as the effects of using different chiral initiators.[57] The polymerization of diphenyl-2-pyridylmethyl methacrylates (D2PyMA) (**3b**) yielded optically active polymers; however, the optical activities for the polymers were approximately 4 times lower than the optical activity of the one-handed poly(TrMa) (**3a**), except when the chiral initiator (+)-1-(2-

pyrrolidinylmethyl)pyrrolidine (PMP) (**3c**) was used.[58-63] Although the chiral initiator PMP gave a one-handed helix, the polymer was incapable of being used in separations, because a loss of optical activity occurred due to the ability of the helices to mutarotate.[64] Further, PMP was found to be a selective initiator in the polymerization of a variety of bulky methacrylates.[65-68]

In an effort to make a more durable helical polymer, 1-phenyldibenzosuberyl methacrylate (PDBSMA) (**3d**) was synthesized by anionic and radical polymerization to give an isotactic polymer.[46,69] Chiral initiators were used to polymerize PDBSMA (**3d**) to a single-handed helix, giving a polymer with higher optical rotary power than poly(TrMA) (**3a**). Okamoto *et al.*[70] expanded this work to the polymerization of (1-methylpiperidin-4-yl) diphenylmethyl methacrylate (MP4DMA) (**3e**), which has a tertiary amine in the side chain allowing for possible interactions of the monomers with the chiral catalysts through hydrogen bonding. Poly(MP4DMA) (**3e**) has twice as long a half-life towards ester hydrolysis as poly(TrMA) (**3a**) and poly(PDBSMA) (**3c**) in MeOH, which is important if the polymer is to be used in HPLC as a chiral stationary phase. Poly(MP4DMA) (**3e**) was successfully polymerized using chiral anionic and radical initiators to give optically active polymers; however, similar to poly(D2PyMa) (3b) the optical activity in solution decreased with time due to helix-helix mutarotation.

Chiral Polyolefins with Aromatic Side Chains

Polystyrene Derivatives

Many chiral polyolefins have been prepared by the attachment of chiral substituents to the para[71-76] and ortho[77] positions of polystyrene (Figure 1-4).[1] For example, Ciardelli *et al.*[73] prepared the polystyrene derivative (*S*)-p-sec-butylstyrene (**4a**) using the radical initiator AIBN and Ziegler-Natta catalysts; however, the latter gave only low molecular weight polymer due to the lower reactivity of the substituted styrenes compared to styrene using Ziegler-Natta catalysis. The resulting amorphous polymer showed no sign of secondary structure formation. Carlini and coworkers synthesized polymers with phenyl groups bound to the chiral center, which were located at the β (**4b**) and γ (**4c**) positions relative to the backbone of the polymer.[78] Similar to earlier findings for chiral vinyl polymers, the polymers with the chiral center in the β position were crystalline and isotactic with increased optical activities, whereas polymers with the chiral center in the γ position were amorphous and appeared atactic.[79] Monomers with phenyl groups in the 2 position of the vinyl group and chiral alkyl ethers in the 1 position (**4d**) have been synthesized by Vuković *et al.*[80] The polymers were random, yet crystalline polymers, with optical activities 2-4 times larger than the monomer, which can be explained by asymmetric induction of the carbon atoms of the polymer chain. Detailed information on polystyrene derivatives was discussed in a review by Ciardelli *et al.*[81]

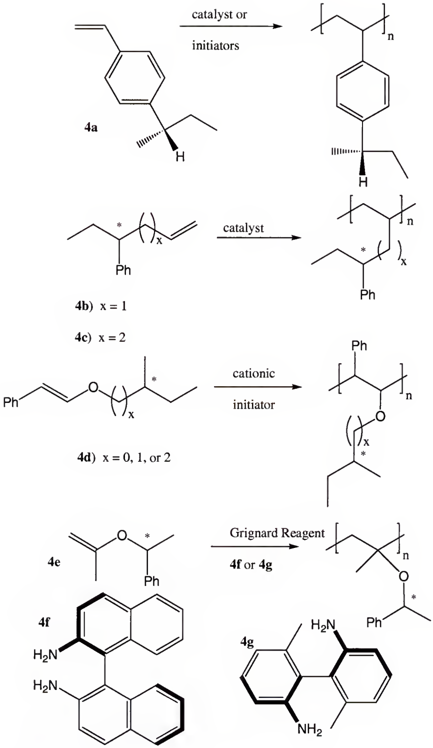


Figure 1-4. Chiral Polystyrene derivatives.

In an attempt to stereoelectively polymerize racemic α-methylbenzyl methacrylate, Sudah and coworkers[82] examined the use of Grignard reagents with axially dissymmetric additives (Figure 1-4). Racemic α-methylbenzyl methacrylate (**4e**) was polymerized with cyclohexylmagnesium bromide and the chiral additive (*R*)-6,6'-dimethyl-2,2'-biphenylylenediamine (**4f**) to yield a polymer with up to 90 % optical purity.[82] To find a more stereoelective reaction, polymerization of the racemic monomer with [1,1'-binaphthyl]-2,2'-diamine (**4g**) and various Grignard reagents was studied.[83] Stereoregularity of 100 % isotacticity for racemic α-methylbenzyl methacrylate (**4e**) was achieved for the first time, and the polymers had optical purities above 83 %. The reaction was best catalyzed using Grignard reagents with Br as the halogen; and a temperature range between –40 °C to 0°C was optimal for both reaction rate and selectivity.

Bulky Chiral Aromatic Substituents

Nakano *et al.* recently explored bulky, chiral substituents in an effort to prepare stereoelective polymers that form helices (Figure 1-5).[84,85] The polymerization of (-)-trans-4,5-bis-((methacryloyloxy)diphenylmethyl)-2,2-dimethyl-1,3-dioxacyclo-pentane (**5a**), which is based on the chiral molecule (-)-trans-4,5-bis(hydroxydiphenylmethyl)-2,2-diemthyl-1,3-dioxacyclopentane — an efficient ligand for asymmetric synthesis[86-88] — yielded a highly isotactic polymer that had higher optical activity than the monomer with a different C.D. spectra.[84] Changes in CD spectra were due to helical formation, which agrees with the findings discussed previously. Further work included the preparation and polymerization of enantiopure and racemic 10,11-*O*-isopropylidene-trans-10,11-dihydroxy-5-phenyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl methacrylate

(IDPMA) (**5b**) with anionic and radical initiators.[85] The polymerization was stereoelective when anionically polymerized, and demonstrated stereoelective tendencies for radical polymerization. This was an impressive finding, because the only other polymer previously reported to be stereoelective for radical polymerization was phenyl-2-pyridyl-o-tolylmethyl methacrylate (PPyoTMA) (**5c**).[89] Poly(IDPMA) (**5b**) was greater than 99 % isotactic for both types of polymerization.[85]

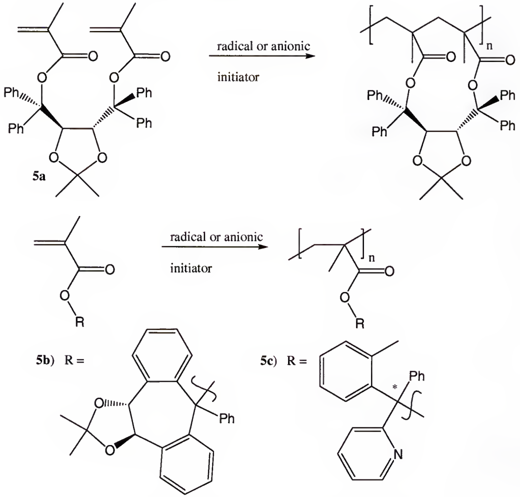
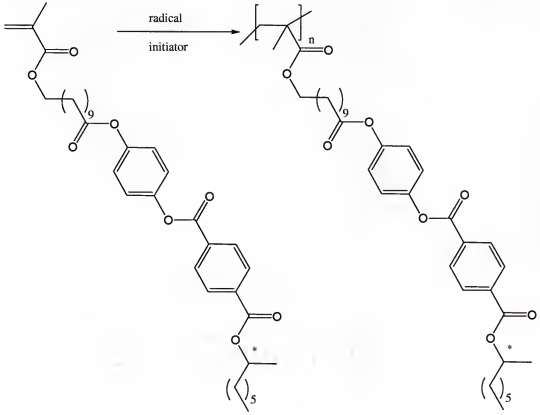


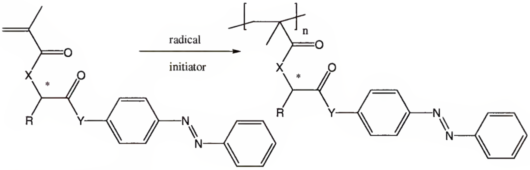
Figure 1-5. Chiral polyolefins with bulky chiral aromatic substituents.

Chiral Aromatic Chromophore Substituents

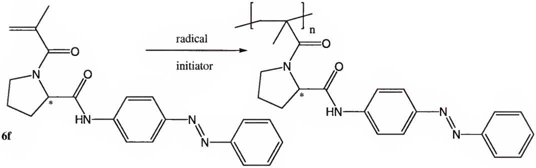
Possible applications for chiral polyolefins bearing aromatic branches are reversible optical storage, chemical photoreceptors, ferroelectronic devices, and in general, nonlinear optical (NLO) applications (Figure 1-6).[90,91] To prepare ferroelectric polymers, 4-(11-methacryloyloxy-undecanoyloxy)-phenyl-4'-(1-(*S*)-methylheptyloxy-carbonyl)-benzoate (**6a**) was polymerized by radical polymerization to yield a polymer that had a smectic type layered lattice as proven by X-ray scattering.[92] The polymer formed transparent films with no birefringence, which could be explained if the polymer was primarily amorphous with some smectic structure, but the polymer had no ferroelectric properties.

6a

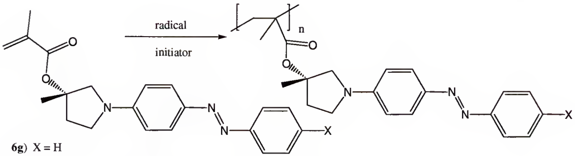




6b) X = O, Y = NH, R = CH_3
6c) X = NH, Y = NH, R = CH_3
6d) X = NH, Y = NH, R = $CH_2CH(CH_3)_2$
6e) X = NH, Y = NH, R = $CH(CH_3)_2$



6f



6g) X = H
6h) X = NO_2
6i) X = CN
6j) X = CHO
6k) X = CH=C(CN)(SO_2CH_3)
6l) X = CH=C$(CN)_2$

Figure 1-6. Polyolefins bearing chiral aromatic chromophores.

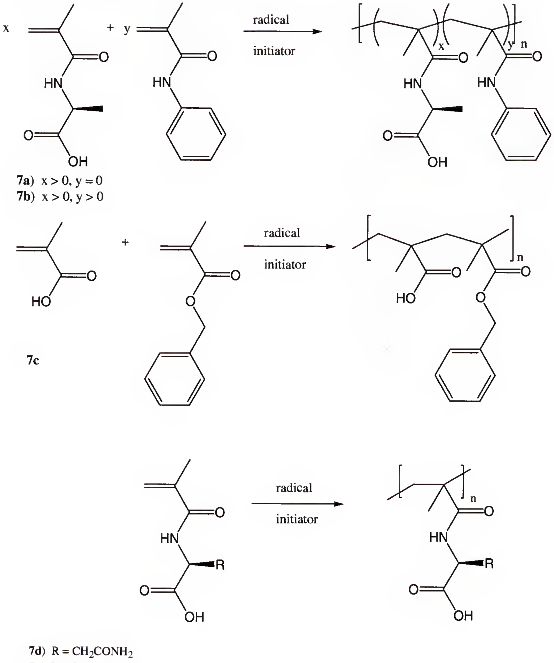
Angiolini *et al.*[93-96] synthesized a variety of chiral polymers bearing azoaromatic chromophores. They attached trans-azobenzene to methacrylic acid through L-lactic acid (MLA) (**6b**) and L-alanine (MAA) (**6c**) residues.[97-99] A chiral perturbation on the electronic transitions of the chromophores were observed, because of the conformational dissymmetry and one-handedness of the polymer for poly(MLA) (**6b**). Unfortunately, poly(MAA) (**6c**) lacked the appropriate CD spectrum that would suggest secondary structure formation; however, Carlini *et al.*[100] have prepared polymers with a photochromic group, trans-azobenzene, separated from the vinyl group by L-leucine (MLEA) (**6d**), L-valine (MVA) (**6e**), or L-proline (MPA) (**6f**). The poly(MVA) (**6e**) and poly(MPA) (**6f**) form a single screw conformation as is evident by CD spectroscopy; whereas, the poly(MLEA) (**6d**) moiety showed no difference in CD spectra compared to that of a model compound. This was explained by the extra methylene group located between the isopropyl group and the amino acid backbone, which could allow for extra mobility of the side chain and thus inhibiting asymmetric induction of the polymer backbone.

This work was extended to polymers having a more rigid structure connecting the azobenzene to the polymer backbone. The polymerization of (*S*)-3-methacryloyloxy-1-(4-azobenzene) pyrrolidine ((*S*)-MAP) (**6g**) and (*S*)-3-methacryloyloxy-1-(4'-nitro-4-azobenzene) pyrrolidine ((*S*)-MAP-N) (**6h**) yielded polymers that form a one-handed helix, showing extended conjugation of the aromatic chromophores compared to model compounds.[93] The polymers had unusually high glass transition temperatures of 169 °C and 208 °C for poly((*S*)-MAP) (**6g**) and poly((*S*)-MAP-N) (**6h**) — temperatures much higher than comparable methacrylic polymers and above the 160 °C temperature desired for NLO applications.[95,101,102] Further, the functional group on the azobenzene was changed by polymerizing (*S*)-3-methacryloyloxy-1-(4'-cyano-4-azobenzene) pyrrolidine ((*S*)-MAP-C) (**6i**), 3-methacryloyloxy-1-(4'-formyl-4-azobenzene) pyrrolidine ((*S*)-MAP-F) (**6j**), 3-methacryloyloxy-1-(4'-(β-cyano-β-(methylsulfonyl)vinyl)-4-azobenzene) pyrrolidine ((*S*)-MAP-S) (**6k**), and (*S*)-3-methacryloyloxy-1-(4'-(β,β-dicyano-vinyl)-4-azobenzene) pyrrolidine ((*S*)-MAP-D) (**6l**), which resulted in polymers with properties similar to those described for poly((*S*)-MAP) (**6g**) and poly((*S*)-MAP-N) (**6h**).[96]

Chiral Polyolefins Bearing Branched Amino Acids

Amino acids are the chiral building blocks of proteins. Being naturally abundant in an enantiopure form, amino acids have been widely used as chiral substituents in polymers.[4,103-105] The resulting polymers have interesting properties due to hydrogen bonding that occurs between the amino acid units. The monomers can be easily prepared from acrylates and methacrylates by simple amide coupling reactions, and radically polymerized to yield chiral polyolefins.[4]

Derivatives of polymethacrylates with an L-alanine branch have been synthesized and studied in great detail.[106-110] Polymethacrylic acid has a compact structure in water, which can be extended to a coil conformation by increasing the ionic nature of the polymer, due to Van der Waals interactions between the methyl groups of the polymers.[111] Thus, copolymers of N-methacryloyl-L-alanine (**7a**) and *N*-phenylmethacrylamide were prepared (Figure 1-7) (**7b**), and the conformation of the polymers in water was studied.[106,107] Copolymers of methacrylic acid and *N*-phenylmethacrylamide demonstrate an increased stability of the compact structure confirmation in water than polymethacrylic acid.[112] However, poly(*N*-methacryloyl-L-alanine) (PNMA) (**7a**), a polymer with a similar structure as polymethacrylic acid (PMA), does not form a compact structure in water unless it is copolymerized with the hydrophobic monomer *N*-phenylmethacrylamide (**7b**). The copolymers were compared to copolymers of methacrylic acid and benzyl methacrylate (**7c**), a polymer of similar structure with known properties, and the two polymers have vastly different properties.[106,107]



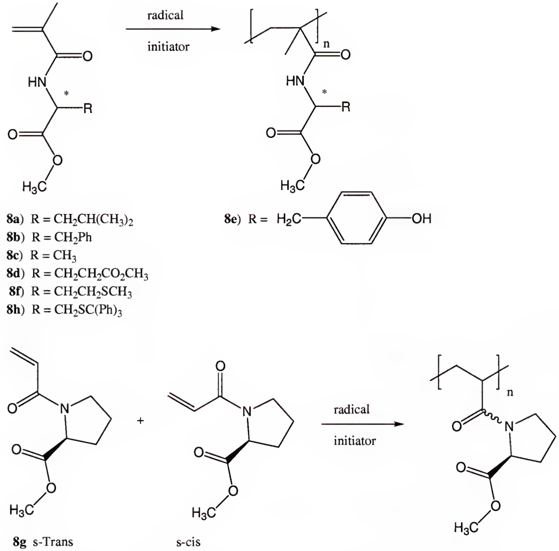
7a) x > 0, y = 0
7b) x > 0, y > 0

7c

7d) R = CH_2CONH_2
7e) R = CH_2Ph

Figure 1-7. Chiral polyolefins bearing amino acids prepared by Morcellet *et al.*[113,114]

To investigate binding properties of poly(*N*-methacryloyl-L-alanine) (**7a**) with Cu(II), a comparison of the binding ability of the alanine branched polymer with the model compound *N*-isobutyroyl-L-alanine was performed.[113,114] Results showed that the model compound formed a weak pH dependant 1:1 ligand:metal complex through the carbonyl anion, whereas the polymer formed a pH-dependant 1:1 and 2:1 ligand:metal complex through one deprotonated nitrogen and between two deprotonated nitrogens of the amide groups respectively. Further, poly(*N*-methacryloyl-L-asparagine) (**7d**) was synthesized along with the model compound, *N*-isobutyroyl-L-asparagine.[115] The presence of a carboxylic acid, secondary amide, and primary amide functionality in the compounds gave results similar to those for the model compound. However, the polymer formed three different copper complexes: complexation between two carboxylate anions from two different branches, complexation between two deprotonated amide nitrogens of two different branches, and complexation between the carboxylate anion and the deprotected amide of the same branch.[115] To determine the binding ability of more hydrophobic amino acid-based polymers, poly(*N*-methacryloyl-L-phenylalanine) (**7e**) was synthesized.[116] Even with the compact conformation of the polymer, results were similar to those for the hydrophilic polymers.



8a) R = $CH_2CH(CH_3)_2$
8b) R = CH_2Ph
8c) R = CH_3
8d) R = $CH_2CH_2CO_2CH_3$
8f) R = $CH_2CH_2SCH_3$
8h) R = $CH_2SC(Ph)_3$

8e) R =

8g s-Trans

s-cis

Figure 1-8. Chiral polyolefins bearing amino acids prepared by Endo *et al.*[117-131]

Endo *et al.* synthesized the L-leucine branched polyolefin, poly(*N*-methacryloyl-L-leucine methyl ester) (PMALM) (**8a**) (Figure 1-8).[117,118] The polymer was of interest due to the useful properties of poly(L-leucine), which can form an α-helix by itself, leading to uses such as artificial skin.[119] PMALM (**8a**) was found to have a large increase in optical activity suggesting a possible induction of chiral secondary structure. The racemic monomer has also been polymerized, and the polymer containing equimolar amounts of enantiomers had a higher T_m, lower T_g, and greater solubility than the homopolymers, which was attributed to intermolecular hydrogen bonding between the D and L enantiomers.[120] Endo and coworkers[121] synthesized acrylamides and methacrylamides bearing a variety of amino acid substituents including L-leucine (**9a**), L-phenylalanine (**8b**), L-alanine (**8c**), L-glutamic acid (**8d**), and L-tyrosine (**8e**). The monomers were polymerized via radical polymerization yielding optically active polymers, which did not show any direct evidence of higher ordered structure formation by CD spectroscopy.

Endo and coworkers[122,123] expanded this work to include peptide branched polymers (Figure 1-9). The dipeptide branched acrylamide *N*-methacryloyl-L-leucyl-L-alanine methyl ester (MALAM) (**9a**), a dipeptide that plays an important role in secondary structure formation has been synthesized. The rate of polymerization of MALAM (9a) was much greater than that of MALM (**8a**), which was explained due to the effect of aggregation of the dipeptide functionality. To investigate the affects of methylene spacers between the amide of the acrylamide and the amino acid moiety, the monomers *N*-(methacryloylglycyl)-L-leucyl-L-alanine methyl ester (MAGLAM) (**9b**) and *N*-(methacryloyl-β-alanyl)-L-leucyl-L-alanine methyl ester (MAβLAM) (**9c**) were synthesized.[124] The polymerizability increased in the order of MAGLAM (**9b**) > MAβLAM (**9c**) > MALAM (**8a**), which was attributed to the degree of aggregation of the polymers. CD spectra for the polymers were similar to that of model compounds; no secondary structure formation is observed. In addition, they synthesized an acrylamide bearing the peptide *N*-acryloyl-12-aminolauryl-L-leucy-Lalanyl-(L-leucyl-L-alanyl-L-leucyl-aminoisobutyryl)$_3$-L-leucyl-L-alanine methyl ester (**9d**).[125] The peptide consists of L-leucine, L-alanine, and α-aminoisobutyric acid; a sequence shown to stabilize helical structures.[126-128] When the radical polymerization was run in chlorobenzene, a CD spectrum similar to that of the monomer was achieved. However, polymerization in the highly polar solvent DMF yielded CD spectra missing the signal at 208 nm; the polymerization in chlorobenzene kept the helical structure in the side chain, whereas the polymerization in DMF destabilized the helical structure.[125]

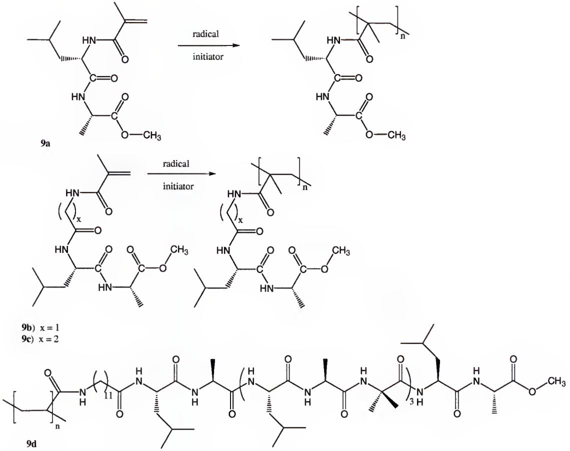
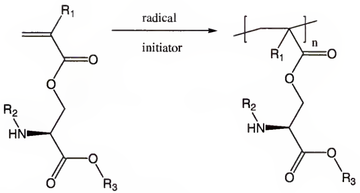
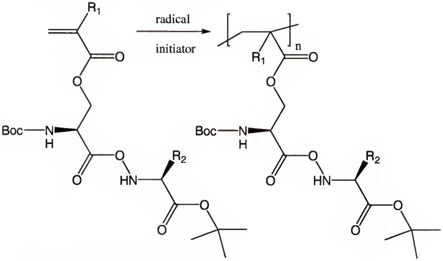


Figure 1-9. Chiral polyolefins bearing peptides prepared by Endo et al.

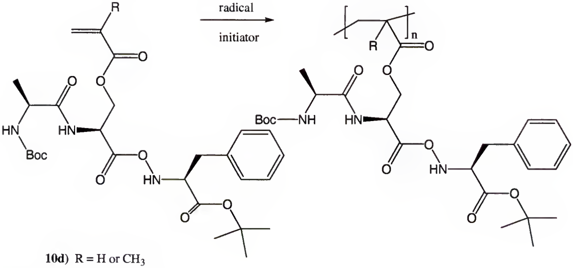
Endo and coworkers also synthesized polymers bearing methionine (**8f**), proline (**8g**), and cysteine (**8h**) moieties (Figure 1-8).[129-131] Polymethionine has high biocompatibility, which should make polymers containing methionine very useful in biomaterial applications. The monomers (**8f**) were radically polymerized, followed by the oxidation of the sulfides to sulfoxides and sulfones with hydrogen peroxide. The monomers were also oxidized first, then polymerized to yield a polymer with the same thermal characteristics as the previous method.[129] The proline containing monomer *N*-acryloyl-L-proline methyl ester (**8g**) was studied to determine the effects of the cis and trans isomers on the polymerization and properties of the resulting polymer.[130] The polymerization temperature greatly affects the cis/trans content of the polymers; the lower the temperature the less cis content — less cis content than was found in the monomer — and the higher the temperature, the more cis content, and the lower the yields of polymer. *N*-methacryloyl-*S*-trityl-L-cysteine methyl ester (**8h**), a monomer bearing the amino acid cysteine, was radically polymerized, copolymerized with methyl methacrylate, and copolymerized with trityl methacrylate.[131] The copolymers demonstrated a nonlinear increase in optical activity with increased chiral monomer incorporation; however, the CD spectrum did not show evidence of a higher ordered structure such as a α-helix. The nonlinear increase in optical activity was therefore attributed to an asymmetric induction of chiral centers in the polymer backbone.[131] Deprotection of the thiol groups with HBr/CH_3CO_2H yielded an insoluble polymer due to crosslinking of the thiol groups; however, the use of $(CH_3CO)_2O$-HBr/CH_3CO_2H yielded a soluble polymer with partially acetylated thiol groups.



10a) R_1 = H or CH_3, $R_2 = C(Ph)_3$, $R_3 = CH_3$
10b) $R_1 = CH_3$, $R_2 = COOCH_2Ph$ (BOC)



10c) R_1 = H or CH_3, $R_2 = CH_3$ or CH_2Ph



10d) R = H or CH_3

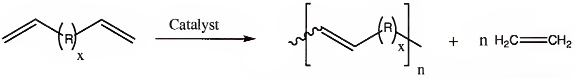
Figure 1-10. Serine based chiral polyolefins prepared by North *et al.*[132]

Serine, an amino acid containing a primary alcohol in the side chain, has been attached to acrylic acid and methacrylic acid through the primary alcohol of the amino acid side chain giving a monomer with protected carboxylic acid and amine functionalities (Figure 1-10) (**10a**).[132] Radical polymerization as well as copolymerization with methyl methacrylate was investigated, resulting in polymers that showed a nonlinear increase in optical activity with up to 10 percent incorporation of chiral monomer. In addition, North and coworkers[133] investigated the properties of the deprotected amine polymer, and have performed CD measurements on copolymers with methyl methacrylate. The CD results indicate that the nonlinear increase in optical activity was observed due to asymmetric induction of new chiral centers during the polymerization, but no evidence for secondary structure formation was observed. It was suggested that the asymmetric induction was due to the use of triphenyl methyl protecting groups, a phenomenon observed for acrylates with bulky substituents.[3]

Polymerization of a serine bearing monomer with acid-labile protecting groups on both the amine and carboxylic acid functionality yielded a polymer that could be easily deprotected (**10b**).[134] The copolymerization with methyl methacrylate showed a nonlinear increase in optical activity with up to 35 percent chiral monomer incorporation, followed by a decrease in optical activity down to a negative rotation at 70 percent chiral-monomer incorporation. The optical activity of a model compound was negative as well, which suggests the positive optical rotation observed was due to asymmetric induction along the backbone of the polymer, and the negative optical activity observed was due to the presence of the serine unit. North and coworkers have extended this study to include serine-based methacrylates bearing di (**10c**) and tripeptides (**10d**).[135] The resulting polymers show similar optical activity behavior when copolymerized with methyl methacrylate as the previously discussed serine branched methacrylate polymers.

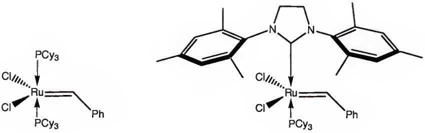
Applying ADMET towards the Synthesis of Bio-Olefins

Acyclic Diene Metathesis (ADMET) involves the reaction of an α,ω diene with a metal (W, Mo, Ru) carbene to yield an unsaturated polyolefin as shown in Figure 1-11.[136-139] ADMET has been reviewed in detail recently; thus, only an overview will be described herein.[139-142] Initially ADMET was limited in its versatility due to catalysts that were functional group intolerant. However, with the advent of Grubbs' 1st (**C1**) and 2nd (**C2**) Generation Ru Catalysts (Figure 1-12), which show a remarkable ability to tolerate most functional groups, metathesis has become a raging field with almost limitless potential.[143-146]



R = Branch point or a variety of functional groups.

Figure 1-11. General ADMET reaction scheme.



C1 **C2**

Figure 1-12. Grubbs' 1st and 2nd Generation Ru catalysts.

Originally, it was a goal in the Wagener group to prepare chiral polymers using ADMET, but the challenge of preparing chiral hydrocarbon-based monomers proved too difficult. The development of the 2nd Generation Grubbs' catalyst caused this goal to be reevaluated. Specifically, work by Endo, Sanda, and Koyama,[131,147] which involved the radical polymerization of a chiral, amino alcohol-based α,ω diene with dithiols (Figure 1-13), motivated the pursuit of amino acid based ADMET polymers.

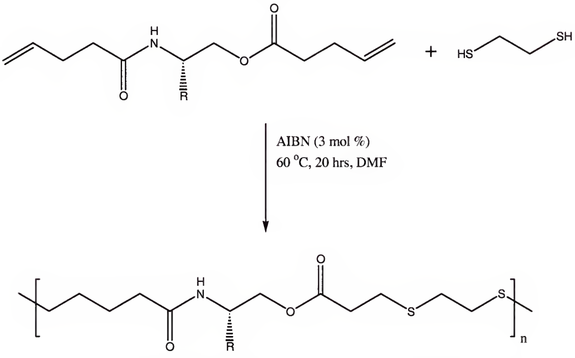


Figure 1-13. Chiral amino alcohol-based polymers prepared by Endo and Sanda.

This document describes the first synthesis of Bio-olefins, a term coined by Professor Seiichi Tokura. The initial polymers that were prepared resemble those of Endo and coworkers,[147,148] and the success of this part of the research has extended to another graduate students main research — only the initial work in this area is reported. The main focus of this document is on the preparation of chiral, branched, and potentially biologically active polyolefins. Amino acid and peptide-branched polymers have been prepared with the amino acid/peptide attached through the *C*-terminus[149] and the *N*-terminus.[150] We have extended this methodology to the preparation of a GRGD (glycine-arginine-glycine-aspartic acid) branched polymer, which if successfully prepared will be tested for biological activity through a collaboration with Professor Sinskey at M.I.T.

CHAPTER 2
INTERNAL AMINO ALCOHOL-BASED BIO-OLEFINS

Introduction

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Acyclic diene metathesis (ADMET) is a straightforward step polymerization that leads to precise structure control.[136-138] Indeed, a variety of polymers, incapable of preparation by any other method, have been prepared using this chemistry.[151-153] As discussed in the previous chapter, chiral polymers, specifically chiral polyolefins, are of major interest. Initial attempts in the Wagener research group to prepare chiral polymers focused on the synthesis of chiral, completely hydrocarbon monomers — hydrocarbon monomers were necessary due to the lack of functional group tolerance of the early metathesis catalysts; however, the task proved very difficult leading to the pursuit of other options for chiral monomers.

Recently, Koyama, Sanda, and Endo polymerized an α,ω diene possessing a chiral internal amino acid moiety via radical polymerization with a dithiol.[147] During the same time period a major advancement occurred for metathesis chemistry; the development of the second generation Grubbs ruthenium catalyst (**1**) (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]-[benzylidene]ruthenium-(IV)di-chloride).[143-146] Unlike previous metathesis catalysts, **1** displayed an amazing tolerance to a wide variety of functional groups. Therefore, the answer to how to prepare chiral polymers by ADMET had been answered: use Mother Nature's source of chiral molecules (amino acids) to prepare a variety of chiral monomers.

Further, the preparation of chiral ADMET polymers using amino acids or amino alcohols gives the added biological benefits such as biocompatibility and biodegradability. Also, amino acid-based chiral polymers can have induced crystallinity, enhanced solubility characteristics, and the ability to form higher ordered structures.[135] These properties result in polymers that are ideal candidates for drug delivery systems, biomimetic systems, biodegradable macromolecules, biomaterials, and as chiral purification media.[4,135,154]

Herein we describe the synthesis of chiral poly(ester amides), termed linear bio-olefins, possessing internal amino alcohol moieties at precise locations (Figure 2-1). In addition, the polymers possessing amino alcohol units in the backbone will likely be biodegradable through the amide and ester bonds.[147,155-157] Further, altering the "regularity" of placement of amino alcohol functionality is easy to do, either via monomer design or by simple copolymerization. As a result, creating an exact molar concentration of amino alcohol groups within the material is easy to accomplish, and this chapter reports our initial work in this area.

Experimental

Chemicals

Chemicals were purchased from the Aldrich chemical company, unless otherwise noted. THF was used as received from Fisher Scientific, unless it is stated that dry THF was used then it was distilled over Na/K. Methylene chloride and chloroform were used as purchased from Fisher, unless it is noted that the solvent was dry then the solvents were refluxed and distilled over CaH_2. Triethylamine was purchased from Aldrich and purified by distillation over CaH_2. Methanol was used from Fisher as received; however, when dry methanol was required it was used as purchased from an Aldrich sure seal bottle. The 2nd generation Grubbs' Ru catalyst (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride) was used exclusively and was synthesized as described previously by Grubbs *et al.*[158]

Instrumentation

All ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Associates Gemini 300, Varian Associates VXR 300, or a Varian Associates Mercury 300 spectrometer. All chemical shifts were referenced to TMS (0.00 ppm) for ^1H NMR and $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.51 ppm) for ^{13}C NMR.

Gel permeation chromatography (GPC) of the unsaturated ADMET polymers was performed using two 300 mm Polymer Laboratories 5μm mixed-C columns. The instrument consists of a Rainin SD-300 pump, Hewlett-Packard 1047-A RI detector, TC-45 Eppendorf column heater set to 35 °C, and a Waters U6K injector. The solvent used was THF at a flow rate of 1 mL/min, and the samples were dissolved in ACS grade THF (5-8 mg/mL) and filtered before injection. Retention times were calibrated to polystyrene standards purchased from Polymer Laboratories (Amherst, MA).

Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC 7 at a heating rate of 10 °C/min using indium and zinc as calibration standards. Heats of fusion were referenced against indium. The samples were scanned three times to remove recrystallization differences between samples and the results reported came from the third scan. The results are listed in tabular form as well as within the text as T_m (peak melting point) and T_g (glass transition at ½ C_p).

Monomer Synthesis

Synthesis of pent-4-enoic acid 3-methyl-2S-pent-4-enoylamino-butyl ester (2a).[147] Synthesized as described by Endo and coworkers.

Synthesis of pent-4-enoic acid 4-methyl-2*S*-pent-4-enoylamino-pentyl ester (3a).[147] Synthesized as described by Endo and coworkers.

Synthesis of pent-4-enoic acid 3-methyl-2*S*-pent-4-enoylamino-pentyl ester (4a).[147] Synthesized as described by Endo and coworkers.

Synthesis of hex-5-enoic acid 2*S*-hex-5-enoylamino-4-methyl-pentyl ester (3b). Monomer **3b** was synthesized using a method previously described by Endo and coworkers using 5-hexenoic acid in place of 4-pentenoic acid in 16.7 % yield.[147] ^{1}H NMR (300MHz, DMSO-d_6, ppm): δ 0.80(d, 3H), 0.82(d, 3H), 1.12-1.40(m, 3H), 1.50-1.65(m, 4H), 1.92-2.10(m, 6H), 2.25(t, 2H), 3.84(q, 1H), 3.91-4.10(m, 2H), 4.90-5.07(m, 4H), 5.70-5.87(m, 2H), 7.68(d, 1H). ^{13}C NMR (75MHz, DMSO-d_6, ppm): δ 22.3, 23.8, 24.2, 24.8, 25.3, 33.1, 33.3, 33.5, 35.5, 46.0, 55.6, 66.6, 115.7, 116.0, 138.6, 139.0, 172.4, 173.3. Elemental analysis (C,H,N): Theoretical (69.86, 10.10, 4.53) Found (69.22, 10.22, 4.61).

Synthesis of undec-10-enoic acid 3-methyl-2*S*-undec-10-enoylamino-butyl ester (2b). To a stirred solution of undecenyl acid (5 g, 27 mmol) in 50 ml $CHCl_3$ was added L-valinol (1.30 g, 12.6 mmol); 1,3-diisopropylcarbodiimide (DIC) (4.23 ml, 27 mmol); and 4-(dimethylamino)pyridine (DMAP) (0.246 g, 2.16 mmol) at 0 °C in a 100 ml round bottom flask under an argon atmosphere. The mixture was gradually warmed to room temperature and stirred for 24 hrs. The resultant solution, containing urea salts, was filtered and the remaining organic solution was washed successively with 1 M HCl (2 x

20 ml); saturated $NaHCO_3$ solution (2 x 20 ml); and saturated NaCl solution (1 x 20 ml). The organic layer was then dried with $MgSO_4$ overnight, filtered by Büchner filtration, and concentrated to yield a viscous oil. The crude product was purified using a Büchi glasKugelrohr at 125 °C and 0.01 mmHg for 4 hours to remove the low boiling starting materials. Further purification by flash column chromatography (3:1 hexanes:ethyl acetate) yielded the desired monomer (**2b**) (4.72 g, 89 %). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.90-0.97(m, 6H), 1.22-1.44(m, 21H), 1.53-1.68(m, 4H), 1.73-1.88(m, 1H), 2.03(q, br, 4H), 2.17(t, 2H), 2.29(t, 2H), 3.98-4.08(m, 2H), 4.22(q, br, 1H), 4.89-5.04(m, 4H), 5.43(d, br, 1H), 5.73-5.89(m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.9, 19.6, 25.2, 26.1, 76.8, 77.2, 77.7, 34.0, 34.4, 37.2, 53.4, 64.5, 114.3, 139.3, 173.1, 174.2. Elemental analysis (C,H,N): Theoretical (74.43, 11.34, 3.21) Found (74.27, 11.36, 3.43).

Synthesis of undec-10-enoic acid 2*S*-undec-10-enoylamino-4-methyl-pentyl ester (3c). Monomer **3c** was synthesized and purified using the methodology employed for **2b** without glasKugelrohr distillation using undecenyl acid (4.02 g, 22 mmol), L-leucinol (0.89 g, 7.3 mmol), dicyclohexylcarbodiimide (DCC) (3.766 g, 18.3 mmol), and DMAP (0.17 g, 1.46 mmol) to yield 1.23 g of the pure material (38 %). ^{1}H NMR (300MHz, DMSO-d_6, ppm): δ 0.79(d, 3H) 0.84(d, 3H), 1.08-1.37(m, 21H), 1.38-1.60(m, 6H), 1.91-2.06(m, 6H), 2.22(t, 2H), 3.74-3.84(m, 1H), 3.89-4.06(m, 2H), 4.87-5.01(m, 4H), 5.69-5.85(m, 2H), 7.57(d, br, 1H). ^{13}C NMR (75MHz, DMSO-d_6, ppm): δ 22.3, 23.8, 24.8, 25.9, 28.9, 29.0, 29.1, 29.2, 33.8, 45.9, 66.7, 115.3, 139.4, 172.5, 173.5. Elemental analysis (C,H,N): Theoretical (74.78, 11.43, 3.11) Found (74.78, 11.51, 3.14).

Synthesis of undec-10-enoic acid 3-methyl-2*S*-undec-10-enoylamino-pentyl ester (4b). Monomer **4b** was synthesized and purified using the methodology employed for **2b** using undecenyl acid (5.00 g, 27.0 mmol), L-isoleucinol (1.48 g, 12.6 mmol), dicyclohexylcarbodiimide (DIC) (4.23 mL, 27.0 mmol), and DMAP (0.26 g, 2.2 mmol) to yield 4.73 g of the pure material (86 %). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.83-.0.99 (m, 6H) 1.07-1.45 (m, 20H), 1.45-1.71 (m, 7H), 1.96-2.11 (m, 4H), 2.18 (t, 2H), 2.31 (t, 2H), 3.97-4.18 (m, 2H), 4.19-4.32 (m, 1H), 4.87-5.08 (m, 2H), 5.40-5.54 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 11.60, 15.54, 25.15, 25.68, 26.03, 29.11, 29.29, 29.36, 29.44, 29.48, 29.53, 29.56, 34.00, 34.46, 36.42, 37.25, 52.38, 64.35, 114.37, 139.37, 172.98, 174.25. Elemental analysis (C,H,N): Theoretical (74.78, 11.43, 3.11) Found (74.33, 11.44, 3.08).

Polymer Synthesis

Polymerization of Hex-5-enoic acid 2*S*-hex-5-enoylamino-4-methyl-pentyl ester (3b). In an oven-dried 50 ml Schlenk tube equipped with a magnetic stir bar was added catalyst **1** (0.0097 g, 0.0114mmol), and **3b** (0.35 g, 1.13 mmol) under atmospheric conditions. Intermittent vacuum was immediately applied to the flask, at such a rate as to keep a controlled release of ethylene, as is evident by bubbling, at 50 °C for 4 h. After this time, full vacuum (10^{-4} mmHg) was applied and the reaction was stirred for 48 h; followed by an increase in the reaction temperature to 70 °C for an additional 72 h. The reaction mixture was then dissolved in 20 ml CH_2Cl_2 and placed in a 50 mL round bottom flask. Afterward tris(hydroxymethyl)phosphine (THP) solution (1 M in isopropanol, 25:1 equivalents of THP:catalyst, 0.287 ml, 0.287 mmol) and refluxed under Ar for an additional 24 h. Upon cooling to room temperature, the CH_2Cl_2 layer was washed with

D.I. H_2O (2 x 20 ml), 1M HCl (1 x 20 ml), and saturated $NaHCO_3$ (1 x 20 ml) followed by drying over $MgSO_4$ and Büchner filtration to yield polymer **6b**. ^1H NMR (300MHz, DMSO-d_6, ppm):δ 0.80-1.00 (br, 6H), 1.08-1.39(m, 3H), 1.40-1.68(br, 4H), 1.80-2.38(m, 8H), 3.75-4.11(m, 3H), 5.25-5.56(br, 2H), 7.58-7.78(br, 1H) (**Note:** Due to the low molecular weight of the polymer, trace signals at 4.90-5.10 and 5.65-5.92 ppm correlating to monomer were present). ^{13}C NMR (DMSO-d_6): δ 22.1-22.3 (br), 22.7-22.9 (br), 24.7-24.9, 26.0, 31.9-32.0 (br), 32.1-32.2 (br), 33.5-33.5 (br), 35.2, 35.5-35.6 (br), 45.9-46.1 (br), 130.5, 172.5, 173.3.

Polymerization of Undec-10-enoic acid 3-methyl-2*S*-undec-10-enoylamino-butyl ester (2b). Monomer **2b** (1.25 g, 2.95 mmol) was polymerized by the aforementioned methodology used for polymer **6b** with catalyst **1** (5.0 mg, 0.0059 mmol) and purified as above using 1M THP (0.147 ml, 0.147 mmol) to yield polymer **5b**. ^1H NMR (300 MHz, $CDCl_3$, ppm):δ 1.04-1.20(m, 6H), 1.36-1.62(br, 20 H), 1.71-1.87(br, 5H), 1.94-2.06(m, 1H), 2.09-2.24(br, 4H), 2.37(t, br, 2H), 2.49(t, br, 2H), 4.17-4.28(br, 2H), 4.35-4.45(q, br, 1H), 5.48-5.60(br, 2H), 5.73-5.85(br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.6, 19.7-19.9(br), 25.3, 26.3, 29.1-30.5 (m, br), 33.0, 34.6, 37.5, 53.5, 64.8, 130.7-130.8(br), 173.3, 174.4.

Polymerization of Undec-10-enoic acid 2*S*-undec-10-enoylamino-4-methyl-pentyl ester (3c). Monomer **3c** (0.600 g, 1.377 mmol) was polymerized and purified by the method employed for polymer **6b** using catalyst **1**(15.0 mg, 0.017 mmol) and 1M THP (0.44 ml, 0.44 mmol) yielding polymer **6c**. ^1H NMR (300 MHz, $CDCl_3$, ppm):δ 0.88-0.97 (m, 6H), 1.20-1.39(br, 21H), 1.53-1.69 (br, 6H), 1.90-2.06(br, 4H), 2.15(t, br, 2H), 2.31(t, br, 2H), 3.97-4.16(m, 2H), 4.22-4.38(br, 1H), 5.29-5.41(br, 2H), 5.42-

5.55(br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.2-21.3, (br), 22.1, 23.9, 24.1, 24.9, 27.7-28.9(m), 31.7, 33.3, 36.0, 39.9, 45.4, 65.2, 129.5, 171.7, 172.9.

Polymerization of Undec-10-enoic acid 2*S*-undec-10-enoylamino-4-methyl-pentyl ester (4b). Monomer **4b** (0.600 g, 1.377 mmol) was polymerized and purified by the method employed for polymer **6b** using catalyst **1**(15.0 mg, 0.017 mmol) and 1M THP (0.44 ml, 0.44 mmol) yielding polymer **7b**. ^{1}H NMR(300MHz, DMSO-d_6, ppm): δ 0.83-.0.89(m, 6H) 1.04-1.41(m, 20H), 1.42-1.69(m, 7H), 1.87-2.07 (m, 4H), 2.17 (t, 2H), 2.30 (t, 2H), 3.99-4.15 (m, 2H), 4.16-4.29(m, 1H), 5.26-5.42 (m, 2H), 5.49-5.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 11.55, 15.50, 25.11, 25.61, 26.03, 29.31, 29.44, 29.55, 29.80, 32.76, 34.41, 36.33, 37.16, 52.29, 64,31, 130.48, 173.02, 174.18.

Hydrogenation of 7b. To a Parr Bomb reaction vessel was added polymer **7b** (480 mg, 1.13 mmol), which was predissolved in hot ethanol (30 mL), and 10 % Pd(C) (4.80 g, 4.5 mmol). The mixture was then placed in a Parr Bomb, and charged to a pressure of 400 PSI H_2. The reaction was stirred 72 hours at room temperature followed by 24 hours at 40 °C. The reaction was filtered, and then the activated carbon was stirred in chloroform and filtered (3 times). Evaporation of the washings yielded 290 mg of the hydrogenated polymer (~97 % by ^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.83-0.98 (m, 6H), 1.16-1.49(br, 28 H), 1.52-1.90 (br, 5H), 2.17 (t, 2H), 2.28(t, 2H), 3.98-4.11 (br, 2H), 4.23 (q, 1H), 5.55 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.77, 19.53, 25.18, 26.10, 29.41, 29.52, 29.54, 29.63, 29.73, 29.76, 29.79, 29.92, 34.47, 37.26, 53.36, 64.55, 173.14, 174.20.

Results and Discussion

Monomer Synthesis

The monomers **2a**, **3a**, **4a**, and **3b** were synthesized according the procedure by Koyama *et al.*[132] (Figure 2-1). The alkenyl acid was reacted with the coupling reagents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, (EDC·HCl), 1,3-dicyclohexylcarbodiimide (DCC), or 1,3-diisopropylcarbodiimide (DIC) to make the activated ester, then the amino alcohol was added followed by the addition of 4-(dimethylamino)pyridine (DMAP) to catalyze the reaction. For monomers **2b** and **4b**, the unreacted starting materials were removed via Glaskugelrohr distillation at 125 °C under full vacuum (10^{-2} mmHg) for four hours, which led to simplified column chromatography and improved reaction yields.

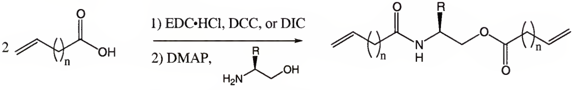
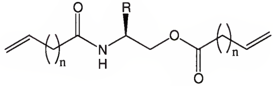


Figure 2-1. General synthetic methodology employed to prepare the linear amino alcohol containing dienes.

Polymer Synthesis

The first amino alcohol based monomers subjected to ADMET conditions were **2a**, **3a**, and **4a**, each of which has two methylene spacers between the terminal olefins and carbonyl groups (Figure 2-2). The polycondensations were performed using a 100:1 monomer to catalyst ratio; however, the observance of ethylene appeared to cease after a short period of time suggesting the metathesis reaction was not occurring. Further, ^{1}H NMR revealed the presence of terminal olefin end groups at 5.5-5.7 and 6.1-6.3 ppm with very little internal olefin formation at 5.7-5.9 ppm verifying a lack of conversion to polymer. Excess catalyst, up to 25:1 monomer:catalyst, was employed to try to overcome this lack of reactivity, but no improvement in molecular weight was observed. It is believed that this lack of reactivity is due to a dynamic intramolecular complexation of the ruthenium catalyst that in turn slows the polycondensation kinetics considerably, a phenomenon which has precedent both for ADMET and ring closing metathesis (RCM) chemistry (Figure 2-3).[158-162]



2a) n = 2, R = $CH_2(CH_3)_2$
3a) n = 2, R = $CH_2CH(CH_3)_2$
4a) n = 2, R = $CH(CH_3)CH_2CH_3$

Figure 2-2. Linear amino alcohol based monomers with 2 methylene spacers between the functionality and the olefins that were not capable of being polymerized

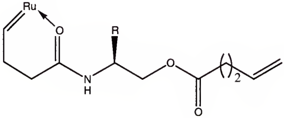


Figure 2-3. Intermolecular complexation as suggested by Ghosh *et al.*[158] to explain the lack of reactivity of monomers **2a**, **3a**, and **4a**.

In RCM this unfavorable complexation was successfully blocked by the addition of a Lewis Acid. For example, the addition of 0.3-3 equivalents of $Ti(O\textit{i}Pr)_4$ has been shown to preferentially complex with carbonyl groups, permitting successful RCM reactions to be observed.[158,160] During our experiments, it became evident that the addition of 2.5 mol % $Ti(O\textit{i}Pr)_4$ produced a product containing significantly more internal olefins by ^1H NMR end group analysis than without $Ti(O\textit{i}Pr)_4$. However, a new multiplet signal at 2.8-3.2 ppm was observed, indicating that a side reaction had occurred (Figure

2-4). Further, GPC analysis showed no increase of molecular weight than when no Ti(O*i*Pr)$_4$ was added under identical conditions. After further examination of the ^{1}H NMR spectrum, it was evident that these observations were due to olefin isomerization. We believe that the reaction temperature used permits Ti(O*i*Pr)$_4$ to isomerize the olefins. In addition to the possibility of the Lewis acid isomerizing the olefin, recent studies in our group have demonstrated that catalyst **1** can isomerizes olefins as well. However, since isomerization was not observed when the polymerization was attempted without Ti(O*i*Pr)$_4$, we feel that the majority of the isomerization is the result of the Lewis acid.

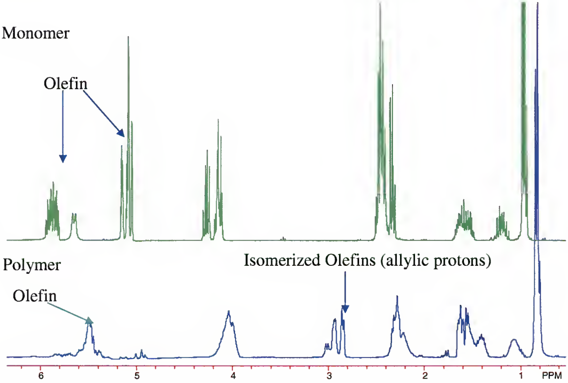
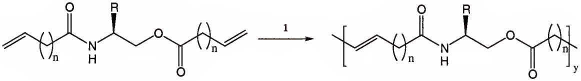


Figure 2-4. ^{1}H NMR of monomer **4a** (green) and the isomerized oligomeric product (blue) using Ti(O*i*Pr)$_4$ as an additive.

In the Wagener group, the answer always employed when polymerization proves difficult is to lengthen the methylene "spacer" between the functionality and the olefin. Intramolecular complexation can be avoided to some extent simply by extending the methylene "spacer" in the monomer from two methylene units to three, as is the case for monomer **3b** (Figure 2-5). This monomer has an L-leucinol moiety with three methylene units between the carbonyl and the olefin sites, and it polymerized to **6b** with a $\overline{M}_n$ of 4700 g/mol, as determined by GPC (Table 2-1). As shown in Figure 2-6, the ADMET reaction is easily monitored by the disappearance of external olefins (4.9 and 5.8 ppm) and the appearance of internal olefins (5.4 ppm). Thus the observance of external olefins in the polymer spectrum (Figure 2-6) is further proof of slower reaction kinetics. The incomplete conversion can be explained by a similar complexation as was observed for **2a**, **3a**, and **4a** forming a 7-membered ring instead of a 6 membered ring, which slows — does not inhibit metathesis — the reaction kinetics leading to a lower molecular weight polymer.



2b) n = 8, R = $CH_2(CH_3)_2$
3b) n = 3, R = $CH_2CH(CH_3)_2$
3c) n = 8, R = $CH_2CH(CH_3)_2$
4b) n = 8, R = $CH(CH_3)CH_2CH_3$

5b) n = 8, R = $CH_2(CH_3)_2$
6b) n = 3, R = $CH_2CH(CH_3)_2$
6c) n = 8, R = $CH_2CH(CH_3)_2$
7b) n = 8, R = $CH(CH_3)CH_2CH_3$

Figure 2-5. General reaction for the synthesis of linear amino alcohol polymers.

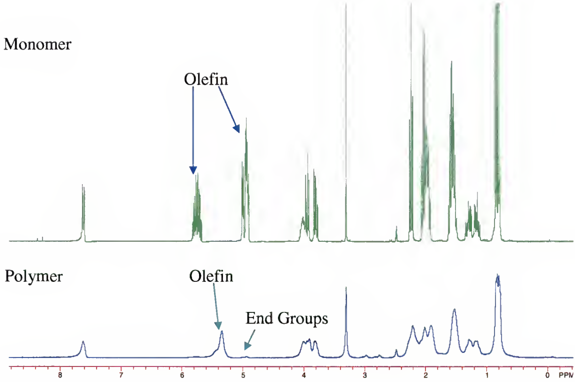


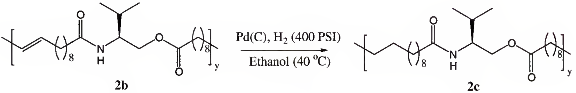
Figure 2-6. The ^{1}H NMR of monomer **3b** and polymer **6b**.

To eliminate the sites of unsaturation along the polymer backbone, polymer **2b** was hydrogenated. This was easily accomplished using Pd(C) as the catalyst in ethanol at 40 °C under 400 PSI H_2 (Figure 2-7). ^{13}C NMR demonstrates the loss of the olefin resonances (Figure 2-8), and ^{1}H NMR demonstrated that the hydrogenation went to approximately 95 % completion. This hydrogenation was not optimized, and it is believed that complete saturation could be achieved by increasing reaction temperature and H_2 pressure. In addition, the polar nature of the polymer made removal from activated carbon difficult causing the reaction yield to be low; the activated carbon had to be stirred in boiling chloroform and filtered multiple times to remove the polymer. This problem could be prevented through the use of a homogeneous catalysts, such as Wilkinson's catalyst.

Monomer	Polymer	$[\alpha]_m$ (°)	$[\alpha]_p$ (°)	$\overline{M}_n$ [a] (g/mol)	PDI[b]	T_m [c] (°C)	T_m [d] (°C)
2b	**5b**	-34	-20	27,000	1.77	29	38
3b	**6b**	-32	-32	4,700	1.73	e	e
3c	**6c**	f	-40	33,000	1.64	e	39
4b	**7b**	-30	f	53,000	1.64	22	39

Table 2-1. Selected characterization data for polymers **5b**, **6b**, **6c**, and **7b**. a) $\overline{M}_n$ values were calculated by GPC versus polystyrene standards. Specific rotations were measured in CH_2Cl_2 at 25 °C, where $[\alpha]_m$ is the specific rotation of the monomer and $[\alpha]_p$ is the specific rotation of the polymer. b) The polydispersity was determined by GPC analysis. c) Determined by DSC. T_m reported is due to melt crystallization. d) T_m reported is due to solution crystallization. e) No T_m was detected in the range of -80 °C to 150 °C. f) No data was collected on this sample.

In an attempt to prevent the intramolecular complexation, more methylene units were placed between the functionality and the olefin. Although it is believed that four methylene units would be large enough to prevent the complexation and yield high polymer, 6-heptenoic acid, which is needed for the monomer synthesis, is not a widely available starting material, so the monomers were prepared with eight methylene units. Monomers **2b**, **3c**, and **4b** were synthesized using the widely available 10-undecenoic acid, having eight methylene units between the functionality and the olefin. (Figure 2-5). These monomers are easily polymerized in the bulk using a 250:1 monomer:catalyst ratio — the ratio was determined to be ideal after trying 100:1, 250:1, and 500:1, where 250:1 gave the highest molecular weight. Polymers **2b** and **3c** had $\overline{M}_n$'s of 27,000 and 33,000 g/mol, respectively, relative to polystyrene. Polymer **4b** was reacted 5, 6, 7, and 10 days, where an average of around 30,000 g/mol was achieved after 5 days, 50,000 g/mol for 6 days, 45,000 g/mol for 7 days, and 20,000 g/mol for 10 days was obtained. This data can be explained by the formation of cyclics, which are common for polycondensations, occurring as the polymerization goes to higher molecular weight. Further, this data demonstrates the long lifetime of catalyst **1**.



2b **2c**

Figure 2-7. The conversion of polymer **2b** to the hydrogenated polymer **2c**.

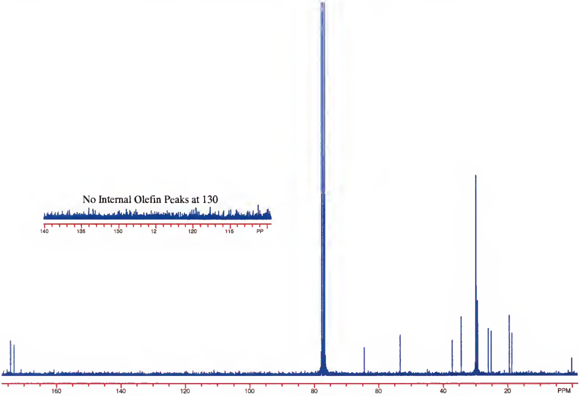


Figure 2-8. The ^{13}C NMR of the hydrogenated version of polymer **4b** showing no internal olefins resonances.

Thermal Properties

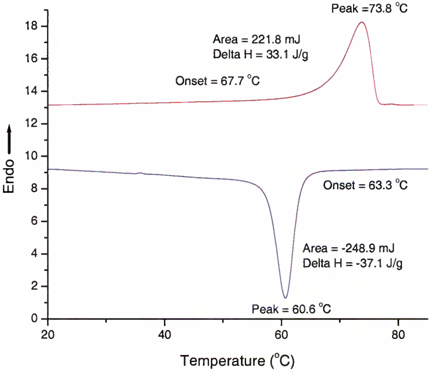


Figure 2-9. The DSC chromatogram of the hydrogenated polymer **2c**.

Differential scanning calorimetry (DSC) was run on the high polymers **2b**, **3c**, and **4b**. The polymers were solvent-cast from chloroform onto a Teflon plate and allowed to air dry till all of the solvent had evaporated. As can be seen in Table 2-1, all of the solvent-cast samples were semicrystalline. The leucinol based polymer **3c** — the most "greasy" — was not semicrystalline from the melt, while polymers **2b** and **4b** demonstrated a lowering of the T_m from solvent evaporated to melt crystallized samples of 9 and 17 °C, respectively. In addition, the hydrogenated polymer **2c** showed an increase in T_m of 40 °C (Figure 2-9), which is a common observation for saturated

ADMET polymers, since the internal olefins (mixture of cis and trans) usually lowers the T_m.

Conclusion

The first ADMET polymerization of monomers bearing amino alcohol functionality is described to give a poly(ester amide)/polyethylene copolymer termed a "linear bio-olefin". Further, the polyethylene run lengths are perfect and dependant only upon the synthesis of the monomers. In addition, the number of methylene units proved to be important, since monomers **2a**, **3a**, and **4a** with 2 "spacers" failed to polymerize due to an intramolecular complexation between the catalyst and the carbonyl functionalities

These linear bio-olefins are film-forming, semicrystalline materials that can be hydrogenated yielding higher melting materials. Further, the resulting polymers should be biodegradable based on the work by Sanda and Endo,[147] and is the subject of ongoing interest in the Wagener research group.

The linear bio-olefins were the first polymers with amino acid-type functionality to be polymerized via ADMET. These polymers or derivatives thereof could potentially be used in drug delivery applications or other biomaterial applications where biodegradability is desired. These linear bio-olefins are currently being studied in detail by Mr. Joshua Priebe, who is addressing the issues of structure/property relationships and biodegradability.

CHAPTER 3
"*C*-TERMINUS" BIO-OLEFINS

Introduction

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The synthesis of polyolefins containing amino acid and peptide branches is a subject of much interest, and can lead to macromolecules forming secondary structures.[4,125] Possible applications include drug-delivery agents, chiral recognition stationary phases, asymmetric catalysts, metal ion absorbents, and biocompatible materials.[113,114] Although initially limited in application by the availability of enantiopure amino acids, advances in the areas of chiral separation and synthesis have produced a variety of inexpensive and enantiopure protected amino acids and small peptides enabling the preparation of a new generation of amino acid-based biomaterials.[4]

For instance, Endo and coworkers have synthesized a variety of amino acid and peptide branched acrylamides via radical polymerizations.[120,122-124,129-131,164] Specifically, a peptide moiety composed of L-leucine, L-alanine, and α-aminoisobutyric acid units, which is known to form a helix, was coupled to methacrylic acid and polymerized to yield a polymer demonstrating the same CD spectrum as the monomer when polymerized using dichlorobenzene as the solvent.[125] Thus, Endo and coworkers reported that the polymer maintained a linear backbone structure with α-helix shaped branches, an important finding since biological activity is usually related to secondary structure. Using a different method of amino acid attachment to acrylates, North *et al.*[132,134]

synthesized a variety of serine-based amino acid branched polymers by radical polymerization, which differ from those of Endo and coworkers since the amino acid functionality is attached to the acrylate through the alcohol of the serine side chain leaving both the *N* and *C*-terminus available for substitution. Further, this methodology was extended to prepare dipeptides and tripeptides attached through the acid and amine of the serine unit.[135]

Grubbs *et al.*[165,166] and North *et al.*[167] have used ring opening metathesis chemistry (ROMP) to make poly(norbornenes) bearing amino acid and peptide branched polymers. The Grubbs' group has extended this work to include the synthesis of polymers bearing the biologically active peptide arginine-glycine-aspartic acid (RGD). A simple copolymerization of a norbornene bearing RGD with a penta(ethylene oxide) branched norbornene yielded a water soluble polymer capable of binding to fibronectin; the RGD based copolymer has potential for a variety of biomedical applications.[168]

Initial work using acyclic diene metathesis (ADMET) to prepare chiral polymers was achieved using amino alcohols incorporated linearly in a polyolefin backbone. However, the resulting polymer resembled a poly(ester-amide) more than a polyolefin (Chapter 2).[148,150] Since the goal of this work was to prepare chiral polyolefins, amino acid branched α,ω dienes were synthesized. We now describe the synthesis of amino acid and peptide branched polyolefins termed "*C*-terminus" bio-olefins — polymers with the amino acid attached to the diene through the *C*-terminus that resemble perfect ethylene-*N*-vinylamide copolymers. The polycondensation mechanism of ADMET enables these polymers to be prepared, since they can't be prepared by common polymerization techniques.[136-138,152,153] *C*-Terminus bio-olefins are strong, film-forming materials possessing moduli of up to 220 MPa with up to 260 % elongation. These polymers are intended to be durable materials possessing hydrophilic surfaces, properties that could prove useful for biomedical applications where biologically compatible materials are desired, *e.g.* coatings for artificial implants. In addition, the attachment of amino acids onto a polyolefin backbone could be advantageous for biomaterial applications, since the resulting polymer backbones are not biodegradable.

Experimental

Chemicals

Chemicals were purchased from the Aldrich chemical company, unless otherwise noted. Diethyl Ether and THF were used as received from Fisher Scientific, unless it is stated that dry solvents were used, which were obtained from the Aldrich keg system and dried over Al_2O_3 or by distillation of the solvent over Na/K. 11-bromo-1-undecene, which was purchased from Fluorochem, 5-bromo-1-pentene, and ethyl formate were refluxed over CaH_2 for 12 hours and distilled prior to use. Methylene chloride and chloroform were used as purchased from Fisher, unless it is noted that the solvent was dry, and then the solvents were refluxed and distilled over CaH_2. Triethylamine was purchased from Aldrich and purified by distillation over CaH_2. Methanol was used from Fisher as received; however, when dry methanol was required it was used as purchased from an Aldrich sure seal bottle. Anhydrous DMF (99.8 %) was used as purchased in an Aldrich sure seal container equipped with an Aldrich Schlenk cap. The 2nd generation Grubbs' Ru catalyst (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV)dichloride) (**C1**)[157] was used in most cases, unless it is noted [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene] [2-(1-methylethoxy)phenyl]methylene]ruthenium(IV)-dichloride

(C2)[170] or tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene][benzylidene]ruthenium(IV)dichloride **(C3)**[171,172] were used, all catalysts were prepared according to the published methods. The protected amino acids and dipeptides were used as purchased from Bachem, except CBz alanine-valine, di-CBz lysine, and di-CBz cysteine, which were purchased from Sigma-Aldrich.

Instrumentation

All ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Associates Gemini 300, Varian Associates VXR 300, or a Varian Associates Mercury 300 spectrometer. All chemical shifts were referenced to TMS (0.00 ppm) for ^{1}H NMR and to $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.51 ppm) for ^{13}C NMR.

Gel permeation chromatography (GPC) of the unsaturated ADMET polymers was performed using two 300 mm Polymer Laboratories 5μm mixed-C columns. The instrument consists of a Rainin SD-300 pump, Hewlett-Packard 1047-A RI detector, TC-45 Eppendorf column heater set to 35 °C, and a Waters U6K injector. The solvent used was THF at a flow rate of 1 mL/min, and the samples were dissolved in ACS grade THF (5-8 mg/mL) and filtered before injection. Retention times were calibrated to narrow polystyrene standards purchased from Polymer Laboratories (Amherst, MA).

Fourier transform infrared (FT-IR) spectrometry was performed using a Bio-Rad FTS-40A spectrometer. The polymers were analyzed by dissolving a small amount of sample into CH_2Cl_2 and allowing the solution to evaporate on a salt plate, and the solid monomers were ground up with IR grade KBr into a homogeneous mixture and analyzed using a KBr pellet formed from the mixture.

Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC 7 at a heating rate of 10 °C/min using indium and n-octane as calibration standards. Heats of fusion were referenced against indium. When possible, the samples were scanned three times to remove recrystallization differences between samples and the results reported came from the third scan. The results are listed in tabular form as well as within the text as T_m (melting peak) and T_g (glass transition at ½ C_p).

Initial stress/strain data was collected on a Instron model 1122 load frame upgraded with an MTS ReNew system running MTS TestWorks 4 software. The tests reported herein were performed using an Instron 500 g load cell.

Characterization

Strenuous purification was only performed on the final monomers reported herein. Only ^{1}H NMR and ^{13}C NMR spectra are reported for the precursors (**3a**, **3b**, and **3c**) to these monomers. The alcohols (**1a**, **1b**, and **1c**) and ketones (**2a**, **2b**, and **2c**) were only isolated in crude form, so no characterization data is given. All of the monomers were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, EI/HRMS, and elemental analysis. The polymers were characterized by ^{1}H NMR, ^{13}C NMR, IR, GPC, and DSC.

Monomer Synthesis

Synthesis of 1-pent-4-enyl-hex-5-enylamine (3a). Magnesium (4.89 g, 0.200 mol) was added to a 500 mL 3 neck flask equipped with a reflux condenser and an addition funnel, and the reaction vessel was backfilled 3 times with Ar and flamed out after the 2nd backfill. Dry ether (100 mL) was added, followed by the dropwise addition 5-bromo-1-pentene (25.0 g, 19.9 mL, 0.170 mol) in 60 mL of dry diethyl ether at such a rate as to maintain a gentle reflux. After the addition was complete, a heating mantle was placed under the reaction vessel and the solution was refluxed for two hours. Ethyl formate (5.64 g, 76.0 mmol) in 20 mL dry diethyl ether was added dropwise to the cooled reaction mixture (0°C), and the solution was allowed to warm slowly to room temperature and refluxed for an additional 12 hrs. Hydrochloric acid (1M, 100 mL) was added and the solution was extracted with ether (3x25 mL), washed with 1M HCl (1x30 mL), and washed with brine (3x20 mL). The solution was dried over $MgSO_4$, followed by evaporation of the solvent to yield 13.6 g of the crude alcohol (**1a**).

To a 1 L round bottom flask equipped with an addition funnel was added pyridinium-chlorochromate (PCC) (26.0 g, 0.12 mol), celite (26.0 g), and methylene chloride (100 mL) followed by the addition of crude **1a** (13.6 g, 0.080 mol) in methylene chloride (20 mL). The reaction was stirred over 4 hours, followed by the addition of diethyl ether (200 mL) and filtering through a pad of silica gel. The solvent evaporation yielded 13.0 g of the crude ketone (**2a**).

To a 1 L round bottom flask was added **2a** (12.96 g, 0.078 mol), dry methanol (200 mL), ammonium acetate (60 g, 0.78 mol), $NaCNBH_3$ (25 g, 0.40 mol), and crushed 4Å molecular sieves (1 scoopula tip) under N_2 and refluxed for 48 hours. The crushed molecular sieves were removed via Büchner filtration, and deionized water (200 mL) was added to the filtrate, followed by extraction with diethyl ether (3x50 mL). The organic layer was washed with 1M NaOH (2x50 mL), brine (2x30 mL), and dried over $MgSO_4$. The solution was concentrated to a viscous brown oil, which was purified by flash column chromatography using a 3:1:1 (hexane:ethyl acetate:methanol) mobile phase yielding the desired product **3a** (9.28 g) for an overall yield of 73 %. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.70 (m, 8H), 2.01-2.15 (br,4H), 2.65-2.76 (br, 1H), 4.90-

5.10 (m, 4H), 5.75-5.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 25.87, 34.29, 37.84, 51.45, 114.95, 139.19.

Synthesis of 1-undec-10-enyl-dodec-11-enylamine (3b). 3b was synthesized as described above using 11-bromo-1-undecene (25.0 g, 0.106 mol) instead of 5-bromo-1-pentene. When purified as above using flash column chromatography, an overall yield of 48% (13.0 g) was obtained. However, it was found that a quick purification of the product can be performed by placing the crude amine on a plug of silica gel and washing with 3:1 hexanes : ethyl acetate (~1 L) until the starting materials are no longer present by TLC. Removal of the amine by washing the plug of silica gel with methanol (~ 1 L) gave **3b** in similar yields. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.45 (br, 32 H), 2.05 (q, br, 4H), 2.65-2.75 (br, 1H), 4.88-5.05(m, 4H), 5.72-5.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.39, 29.20, 29.41, 29.76, 29.84, 29.90, 30.07, 34.08, 38.02, 51.50, 114.36, 139.50.

Synthesis of 1-dec-9-enyl-undec-10-enylamine (3c). Synthesis was performed using a modified procedure by Zantour and coworkers.[169] To a 500 ml 3 neck round bottom flask equipped with a reflux condenser and an addition funnel was added 10-undecenoyl chloride (0.100 mol, 20.27 g, 21.48 mL) and dry diethyl ether (150 mL). The solution was cooled to 0 °C, and triethylamine (0.180 mol, 18.21 g, 25.09 mL) was added dropwise instantly forming white triethylammonium chloride salts. The reaction mixture was warmed to room temperature and stirred for 24 hrs, followed by Büchner filtration of the salts and evaporation to yield the liquid intermediate lactone. D.I. water (100 mL) and NaOH (2.10 mol, 8.80 g) was added and the mixture was refluxed for 6 hours. The solution was acidified with 1M HCl and extracted with diethyl ether (3x40 mL), and the combined organic layers were washed with 1M HCl (2x20 mL), sat. $NaHCO_3$ (2x20 mL), and brine (2x20mL). After drying over $MgSO_4$ and recrystallizing from CH_3OH, the pure ketone (**2c**) (12.58 g, 82 %) was obtained. The ^1H NMR and ^{13}C NMR were in agreement with those reported previously.[169,151]

The ketone **2c** (11.30 g, 36.9 mmol) was converted to the amine **3c** (8.00 g, 70 %) using the same methodology as described above. The overall yield for the two steps was 52 %. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.18-1.62 (br, 28H), 2.04 (q, 4H), 2.80-2.94 (m, br, 1H), 4.03-4.54 (br, 2H), 4.88-5.07 (m, 4H), 5.71-5.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.52, 29.34, 29.54, 29.88, 30.01, 30.20, 34.21, 38.18, 51.61, 114.46, 139.48.

General coupling procedure of the amino acid/dipeptides to 3a/3b/3c. The amino acid/dipeptide and 1-hydroxybenzotriazole (HOBt) (2.5 equiv. to amino acid) were added to a 100 mL round bottom flask. To the flask, equipped with a septum, a stir bar, and under argon, was added 1,3-diisopropylcarbodiimide (DIC) (1.2 equiv. to amino acid) and dry THF (just enough to dissolve the compounds). The reaction vessel was equipped with a reflux condenser and stirred one hour at room temperature, followed by the addition of **3a/3b/3c** (1.1 equiv. to amino acid). The reaction mixture was then refluxed for 12 hours for the amino acids and 24 hours for the dipeptides. The insoluble urea was removed via gravity filtration, and THF was evaporated to yield a crude white solid. The product was purified with 3 successive recrystallizations using ethanol/water or methanol/water (ethanol was used for the monomers that melt above the boiling point of ethanol); the product was dissolved in hot ethanol/ methanol, and water was added till the solution became cloudy. The pure product was then collected by vacuum filtration through a Kontes filtration apparatus and dried under vacuum (10^{-2} mmHg) for 48 hours.

Synthesis of [(*S*)-3-methyl-1-(1-pent-4-enyl-hex-5-enylcarbamoyl)-butyl]-carbamic acid tert-butyl ester (4a). The pure product **4a** was obtained in 78 % yield with a melting point range equal to 117-119 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.85-0.95 (m, 6H), 1.27-1.55 (br, 18H), 1.58-1.72 (br, 2H), 2.05 (q, br, 4H), 3.82-3.92 (br, 1H), 3.95-4.06 (m, 1H), 4.86-5.03 (m, 5H), 5.65-5.83 (m, 2H), 5.88 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.51, 22.96, 24.99, 25.21, 25.28, 25.51, 28.51, 33.71, 33.76, 34.82, 34.88, 41.07, 49.09, 53.55, 114.91, 138.67, 138.70, 156.00, 172.27. FTIR (KBr pellet, cm^{-1}): 3344, 3279, 3083, 2979, 2936, 2869, 1688, 1649, 1561, 1522, 1455, 1392, 1367, 1321, 1294, 1248, 1176, 1121, 1048, 1023, 995, 910, 875, 792, 753, 633. Anal. Calcd. for $C_{22}H_{40}N_2O_3$: C 69.43, H 10.59, N 7.36. Found: C 69.38, H 10.61, N 7.49. EI/HRMS [M + 1]: Calcd for $C_{22}H_{40}N_2O_3$: 380.3039 g/mol. Found: 380.3117 g/mol.

Synthesis of [(*S*)-3-methyl-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-butyl]-carbamic acid tert-butyl ester (4b). The pure product **4b** was obtained in 39 % yield with a melting point range equal of 75-76 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 0.84 (m, 6H), 1.05-1.43 (br, 42H), 1.46-1.64 (br, 2H), 1.98 (q, br, 4H), 3.56-3.71 (br, 1H), 3.88 (q, br, 1H), 4.87-5.03 (br, 4H), 5.68-5.85 (m, 2H), 6.70 (d, br, 1H), 7.34 (d, br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 25.23, 26.22, 26.27, 28.74, 29.39, 29.59, 29.82, 29.94, 30.02, 30.06, 30.08, 30.13, 30.18, 34.21, 34.27, 35.67, 35.73, 35.77, 35.80, 49.65, 114.51, 139.65, 172.17, 174.63. FTIR (KBr pellet, cm^{-1}): 3336, 3291, 2924, 2854, 1690, 1654, 1526, 1468, 1391, 1368, 1326, 1246, 1175, 1055, 913. Anal.

Calcd. for $C_{34}H_{64}N_2O_3$: C 69.43, H 10.59, N 7.36. Found: C 69.38, H 10.61, N 7.49. EI/HRMS [M + 1]: Calcd. for $C_{34}H_{64}N_2O_3$: 548.4917 g/mol. Found: 548.4995 g/mol.

Synthesis of [(*S*)-1-(1-pent-4-enyl-hex-5-enylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (5a). The pure product **5a** was obtained in 76 % yield with a melting point range equal of 77-78 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.27-1.69 (br, 20H), 2.05 (q, br, 4H), 3.82-3.95 (br, 1H), 3.99-4.14 (m, 1H), 4.86-5.03 (m, 5H), 5.65-5.83 (m, 2H), 5.88 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 25.26, 25.30, 28.53, 33.76, 33.78, 34.88, 34.90, 49.18, 114.95, 138.69, 172.38. FTIR (KBr pellet, cm^{-1}): 3340, 3306, 3076, 2981, 2938, 2859, 1688, 1654, 1542, 1522, 1459, 1391, 1370, 1323, 1250, 1167, 1071, 1052, 1031, 999, 910, 856, 754, 701, 674. Anal. Calcd. for $C_{19}H_{34}N_2O_3$: C 67.42, H 10.12, N 8.28. Found: C 67.41, H 10.17, N 8.44. EI/HRMS [M + 1]: Calcd. for $C_{19}H_{34}N_2O_3$: 338.2569 g/mol. Found: 338.2648 g/mol.

Synthesis of [(*S*)-1-(1-dec-9-enyl-undec-10-enylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (5b). The pure product **5b** was obtained in 75 % yield with a melting point range equal of 68-69 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.55 (br, 40H), 2.02 (q, br, 4H), 3.78-3.93 (br, 1H), 4.00-4.18 (br, 1H), 4.88-5.08 (br, 5H), 5.70-5.92 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.02, 28.53, 29.13, 29.32, 29.65, 29.67, 29.71, 29.73, 29.77, 29.80, 34.03, 35.48, 49.50, 114.33, 139.45, 172.18. FTIR (KBr pellet, cm^{-1}): 3333, 3301, 2983, 2925, 2854, 1691, 1656, 1549, 1526, 1468, 1391, 1369, 1325, 1268, 1251, 1174, 1069, 1055, 1031, 992, 908, 858, 792, 757, 721, 701, 654. Anal. Calcd. for $C_{29}H_{54}N_2O_3$: C 72.75, H 11.37, N 5.85. Found: C 72.80, H 11.55, N 5.85. EI/HRMS [M + 1]: Calcd. for $C_{29}H_{54}N_2O_3$: 478.4134 g/mol. Found: 478.4134 g/mol.

Synthesis of [(*S*)-1-(1-dec-9-enyl-undec-10-enylcarbamoyl)-ethyl]-carbamic acid benzyl ester (5c). The pure product **5c** was obtained in 74 % yield with a melting point range equal of 83-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.12-1.55 (br, 31H), 2.02 (q, br, 4H), 3.78-3.92 (br, 1H), 4.09-4.25 (m, 1H), 4.84-5.05 (m, 4H), 5.10 (s, 2H), 5.29-5.42 (br, 1H), 5.66 (d, br, 1H), 5.72-5.89 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.03, 29 (m), 34.03, 35.37, 35.41, 49.66, 50.88, 67.21, 114.35, 128.24, 128.45, 128.78, 139.44, 171.73. FTIR (KBr pellet, cm^{-1}): 32.82, 3081, 2982, 2925, 2854, 1696, 1653, 1557, 1536, 1467, 1323, 1261, 1169, 1072, 1057, 994, 909, 787, 734, 696. Anal. Calcd. for $C_{32}H_{52}N_2O_3$: C 74.95, H 10.22, N 5.46. Found: C 74.91, H 10.35, N 5.46. EI/HRMS [M + 1]: Calcd. for $C_{32}H_{52}N_2O_3$: 512.3978 g/mol. Found: 512.3978 g/mol.

Synthesis of [(S)-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (5d). The pure product **5d** was obtained in 22 % yield with a melting point range equal of 80-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.55 (br, 44H), 2.03 (q, br, 4H), 3.77-3.92 (br, 1H), 4.00-4.16 (br, 1H), 4.89-5.07 (br, 5H), 5.73-5.90 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.02, 28.53, 29.16, 29.34, 29.69, 29.77, 34.02, 35.49, 49.51, 114.31, 139.46, 172.16. FTIR (KBr pellet, cm^{-1}): 3332, 3295, 2924, 2854, 1690, 1656, 1549, 1526, 1468, 1391, 1369, 1325, 1248, 1174, 1070, 1054, 913. Anal. Calcd. for $C_{31}H_{58}N_2O_3$: C 73.47, H 11.54, N 5.53. Found: C 73.53, H 11.60, N 5.27. EI/HRMS [M + 1]: Calcd. for $C_{34}H_{64}N_2O_3$: 506.4447 g/mol. Found: 506.4522 g/mol.

Synthesis of [(S)-5-tert-butoxycarbonylamino-5-(1-pent-4-enyl-hex-5-enyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester (6a). The pure product **6a** was obtained in 55 % yield (mp = 94-95 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.16-1.67

(br, 31H), 1.73-1.89 (m, 1H), 1.92-2.12 (br, 4H), 3.00-3.16 (br, 2H), 3.90-4.12 (br, 2H), 4.50-4.69 (br, 1H), 4.87-5.04 (br, 4H), 5.06-5.23 (br, 1H), 5.65-5.85 (br, 2H), 5.92 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.92, 25.28, 25.32, 28.54, 28.66, 29.92, 31.95, 33.72, 33.76, 34.83, 34.89, 40.09, 49.17, 54.88, 79.32, 114.95, 138.70, 156.03, 156.36, 171.79. Anal. Calcd. for $C_{27}H_{49}N_3O_5$: C 65.42, H 9.96, N 8.48. Found: C 65.61, H 10.12, N 8.43.

Synthesis of [5-tert-butoxycarbonylamino-5-(1-dec-9-enyl-undec-10-enyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester (6b). The pure product **6b** was obtained in 73 % yield (mp = 94-95 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.13-1.66 (br, 51H), 1.72-1.91 (m, 1H), 2.02 (q, 4H), 2.97-3.15 (br, 2H), 3.72-3.90 (br, 1H), 3.95 (q, br, 1H), 4.54-4.65 (br, 1H), 4.86-5.04 (m, 4H), 5.05-5.20 (br, 1H), 5.71-5.91 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.91, 26.05, 28.54, 28.66, 29.13, 29.33, 29.66, 29.73, 29.76, 29.79, 29.92, 32.05, 34.02, 35.43, 40.07, 49.52, 54.86, 79.35, 80.15, 114.34, 139.44, 156.00, 156.36, 171.66. Anal. Calcd. for $C_{27}H_{49}N_3O_5$: C 65.42, H 9.96, N 8.48. Found: C 65.61, H 10.12, N 8.43.

Synthesis of [(*S*)-5-benzyloxycarbonylamino-5-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-pentyl]-carbamic acid benzyl ester (6c). The pure product **6c** was obtained in 47 % yield with a melting point range equal of 111-113 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.91 (br, 37H), 1.95-2.13 (br, 1H), 2.23 (q, br, 4H), 3.25-3.44 (br, 2H), 3.96-4.12 (br, 1H), 4.18-4.33 (br, 1H), 4.91-5.07 (br, 1H), 5.08-5.24 (br, 4H), 5.30 (s, br, 4H), 5.56-5.71 (br, 1H), 5.89 (d, br, 1H), 5.93-6.09 (m, 2H), 7.49-7.60 (br, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.66, 25.97, 29(m), 33.91, 34.12, 35.37, 40.41, 49.59, 55.00, 66.71, 114.29, 128(m), 138.63, 156.49, 171.11. FTIR (KBr pellet, cm^{-1}): 3316, 3278, 2926, 2854, 1691, 1650, 1535, 1467, 1266, 1247, 1153, 1080, 1054, 1024, 911, 696. Anal. Calcd. for $C_{45}H_{69}N_3O_5$: C 73.83, H 9.50, N 5.74. Found: C 73.48, H 9.59, N 5.65. EI/HRMS [M + 1]: Calcd. for $C_{34}H_{64}N_2O_3$: 731.5237 g/mol. Found: 731.5315 g/mol.

Synthesis of [(*S*)-5-tert-butoxycarbonylamino-5-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-pentyl]-carbamic acid tert-butyl ester (6d). The pure product **6d** was obtained in 87 % yield with a melting point range equal of 82-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.17-1.68 (br, 54H), 1.74-1.92 (m, 2H), 2.05 (q, 4H), 3.10 (q, br, 2H), 3.78-3.91 (br, 1H), 3.97 (q, br, 1H), 4.55-4.66 (br, 1H), 4.86-5.05 (m, 4H), 5.06-5.18 (br, 1H), 5.72-5.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.91, 26.07, 28.53-29.92(m), 32.05, 34.03, 35.39, 35.43, 49.53, 114.32, 139.45, 156.35, 172.38. FTIR (KBr pellet, cm^{-1}): 3375, 3342, 3302, 2981, 2926, 2855, 1690, 1653, 1530, 1450, 1391, 1367, 1279, 1250, 1176, 910, 637. Anal. Calcd. for $C_{19}H_{34}N_2O_3$: C 70.54, H 11.08, N 6.33. Found: C 70.57, H 11.16, N 6.12. EI/HRMS [M + 1]: Calcd. for $C_{19}H_{34}N_2O_3$: 663.5550 g/mol. Found: 663.5628 g/mol.

Synthesis of thiocarbonic acid *O*-benzyl ester *S*-[2-benzyloxycarbonylamino-2-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-ethyl] ester (7). The pure product **7** was obtained in 29 % yield with a melting point range equal of 129-130 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15-1.54 (br, 32H), 2.07 (q, br, 4H), 3.13-3.38 (m, 2H), 3.79-3.91 (br, 1H), 4.40 (q, br, 1H), 4.88-5.05 (m, 4H), 5.06-5.18 (m, 2H), 5.18-5.29 (m, 2H), 5.68 (d, br, 1H), 5.73-5.89 (m, 2H), 5.93 (d, br, 1H), 7.35 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.06, 29(m), 33.50, 34.04, 35.24, 49.96, 55.59, 67.46, 69.79, 114.35, 128(m), 135.03, 136.33, 139.44, 156.52, 169.29, 171.72. FTIR (KBr pellet, cm^{-1}): 3278, 2923, 2853, 1712, 1693, 1650, 1561, 1534, 1276, 1241, 1159, 1047, 994, 908, 746, 697. Anal. Calcd. for $C_{42}H_{62}N_2O_5S$: C 71.35, H 8.84, N 3.96. Found: C 71.20, H 8.83, N 3.90. EI/HRMS [M + 1]: Calcd. for $C_{42}H_{62}N_2O_5S$: 706.4379 g/mol. Found: 706.4458 g/mol.

Synthesis of {(*S*)-1-[(*S*)-2-methyl-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-propylcarbamoyl]-ethyl}-carbamic acid benzyl ester (8). The pure product **8** was obtained in 46 % yield with a melting point range equal of 135-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.912 (m, 6H), 1.06-1.55 (br, 33H), 2.02 (q, br, 4H), 2.31-2.57 (br, 2H), 3.47 (q, br, 2H), 3.75-3.93 (br, 1H), 4.15 (t, 1H), 4.86-5.15 (br, 6H), 5.45-5.57 (m, br, 1H), 5.67-5.89 (br, 3H), 6.46 (d, br, 1H), 7.33 (s, br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.48, 19.50, 26.10, 29(m), 31.32, 34.01, 35.13, 35.31, 36.23, 37.50, 49.77, 59.16, 66.18, 114.33, 128.19, 128.24, 128.68, 136.81, 139.40, 170.70. FTIR (KBr pellet, cm^{-1}): 3280, 3080, 2926, 2854, 1690, 1638, 1542, 1468, 1386, 1272, 1151, 1024, 994, 911, 723, 696. Anal. Calcd. for $C_{36}H_{67}N_3O_4$: C 73.20, H 10.24, N 6.57. Found: C 73.05, H 10.28, N 6.30. EI/HRMS [M + 1]: Calcd. for $C_{39}H_{65}N_3O_4$: 639.4975 g/mol. Found: 639.5053 g/mol.

Synthesis of {(*S*)-3-methyl-1-[(*S*)3-methyl-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-butylcarbamoyl]-butyl}-carbamic acid benzyl ester (9). The pure product **9** was obtained in 95 % yield with a melting point range equal of 68-71 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.917 (m, 12H), 1.17-1.79 (br, 47H), 2.03 (q, 4H), 3.75-3.91 (br, 1H), 3.97-4.14 (br, 1H), 4.31-4.43 (m, 1H), 4.86-5.04 (br, 5H), 5.72-5.89 (m, 2H), 5.97-6.10 (br, 1H), 6.47-6.62 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.70, 23.14, 24.98, 26.03, 26.11, 28.49, 29(m), 34.03, 35.18, 35.45, 41.07, 49.58, 52.22, 53.49, 114.31, 139.45, 171.24, 172.67. FTIR (KBr pellet, cm^{-1}): 3290, 3080, 2926, 2854, 1693, 1646, 1532, 1468, 1438, 1391, 1368, 1324, 1292, 1270, 1241, 1175, 1121, 1052, 1021, 993, 966, 912, 875, 792, 747, 720, 667, 570. Anal. Calcd. for $C_{40}H_{75}N_3O_4$: C 72.57, H 11.42, N 6.35. Found: C 72.30, H 11.61, N 6.02. EI/HRMS [M + 1]: Calcd. for $C_{40}H_{75}N_3O_4$: 661.5758 g/mol. Found: 661.5835 g/mol.

Polymer Synthesis

General synthesis. The monomer was added to a 50 or 100 mL schlenk tube equipped with a stir bar and a glass stopcock, and dried by heating the vessel in an oil bath at 50 °C under full vacuum (10^{-3} mmHg) for 24 hrs. After 24 hrs the reaction vessel was backfilled with Ar and the 2nd generation Grubbs' Ru catalyst (100:1/monomer:catalyst) was added, while maintaining a positive Ar flow throughout the system. A septum was placed in the top of the vessel equipped with a syringe needle to allow the Ar to flow through the system and out through a bubbler. A minimal amount of dry THF, just enough to dissolve the polymer, was added via syringe, and the reaction mixture was allowed to stir for 120 hrs. Dry THF was added periodically, due to the loss of THF by evaporation, as to keep the polymer in solution; however, the reaction is difficult to monitor, because the ethylene released is not as easily observed as in the case for bulk ADMET polymerizations. After 120 hours, the reaction was sampled and tested for total conversion by ^{1}H NMR (monitoring terminal olefin disappearance). If incomplete conversion was observed more catalyst was added and the mixture was stirred for an additional 48 hrs. Once it was evident that the polymerization had reached high conversion, the mixture was dissolved in THF or $CHCl_3$ and precipitated into cold methanol, unless it is otherwise noted. The polymers were then dissolved and solvent cast onto a Teflon™ plate to yield a thin film.

Characterization of 10a. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.79-1.02 (m, 6H), 1.14-1.55 (br, 18H), 1.55-1.74 (br, 2H), 1.76-2.06(br, 3H), 2.05-2.42 (br, 1H), 3.73-3.95 (br, 1H), 3.95-4.18 (m, 1H), 4.83-5.98 (br, 1H), 5.17-5.46 (br, 2H), 5.52-5.73 (br, less than 1 H, external olefin?), 5.97-6.26 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.48, 23.14, 23.48, 25.01, 26.03, 27.91, 28.52, 29.79, 31.64, 31.77, 32.68, 35.44, 41.45, 44.55, 44.62, 49.13, 53.51, 124.49, 127.28, 156.00, 171.99.

Characterization of 10b. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.77-0.95 (br, 6H), 1.03-1.50 (br, 42H), 1.51-1.69 (br, 2H), 1.80-2.01 (br, 4H), 3.71-3.87 (br, 1H), 3.88-4.05 (br, 1H), 4.79-5.10 (br, 1H), 5.19-5.30 (br, 2H), 5.72-6.06 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.48, 23.05, 24.88, 28.43, 28.88-31.88 (m), 32.87, 35.48, 41.27, 49.36, 49.57, 130.55, 155.99, 172.11. FTIR (KBr pellet, cm^{-1}): 3285, 2976, 2955, 2854, 1689, 1649, 1526, 1465, 1456, 1437, 1391, 1366, 1320, 1289, 1249, 1174, 1119, 1046, 1023, 967, 921, 875, 800, 721.

Characterization of 11a. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.11-1.58 (br, 20H), 1.85-2.19 (br, 4H), 3.72-3.94 (br, 1H), 4.00-4.29 (br, 1H), 5.14-5.66 (br, 3H), 5.88-6.69 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.71, 26.00, 28.60, 29.07, 30.53, 32.61, 34.74, 49.21, 50.49, 130.52, 155.82, 172.75.

Characterization of 11b. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.09-1.58 (br, 40H), 1.84-2.07 (br, 4H), 3.78-3.94 (br, 1H), 4.06-4.26 (br, 1H), 5.25-5.52 (br, 3H), 6.06-6.34 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.74, 26.07, 27.40, 28.53, 29 (m), 32.78, 35.14, 35.50, 49.46, 50.36, 79.95, 130.53, 155.75, 172.33. FTIR (KBr pellet, cm^-

^{1}): 3424, 3328, 3055, 2984, 2931, 2856, 1705, 1669, 1519, 1497, 1455, 1425, 1392, 1368, 1324, 1266, 1167, 1094, 1067, 1027, 971, 897, 855, 744, 705.

Characterization of 11c. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.96-1.61 (br, 31H), 1.81-2.09 (br, 4H), 3.70-3.95 (br, 1H), 4.12-4.40 (br, 1H), 5.09 (s, br, 2H), 5.25-5.45(br, 2H), 5.65-5.92 (br, 1H), 6.08-6.44 (br, 1H), 7.34 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.38, 26.11, 29 (m), 32.84, 35.33, 35.45, 49.62, 50.84, 67.03, 128.11, 128.37, 128.74, 130.13, 130.59, 136.46, 156.20, 172.06. FTIR (KBr pellet, cm^{-1}): 3422, 3341, 3056, 2988, 2930, 2857, 1718, 1673, 1503, 1454, 1423, 1266, 1068, 972, 897, 743, 705.

Characterization of 11d. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.99-1.61 (br, 44H), 1.48-2.07 (br, 4H), 3.72-3.91 (br, 1H), 3.98-4.19 (br, 1H), 5.02-5.25 (br, 1H), 5.26-5.43 (br, 2H), 5.84-6.13 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.70, 26.07, 28.54, 29 (m), 32.81, 35.49, 49.51, 130.55, 172.33. FTIR (KBr pellet, cm^{-1}): 3425, 3056, 2986, 2930, 2857, 1707, 1673, 1497, 1456, 1423, 1369, 1265, 1167, 1024, 897, 740, 705.

Characterization of 12a. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.69 (br, 30H) 1.69-2.23 (br, 6H), 2.98-3.19 (br, 2H), 3.74-4.17 (br, 2H), 4.73-5.07 (br, 1H), 5.19-5.74 (br, 3H), 6.05-6.67 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.98, 24.66, 26.04, 28.54, 28.60, 28.70, 29.90, 32.07, 32.60, 34.87, 40.29, 49.27, 54.82, 79.23, 79.91, 130.47, 156.11, 156.42, 172.30.

Characterization of 12b. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.08-1.79 (br, 50H), 1.71-2.07 (br, 6H), 2.98-3.16 (br, 2H), 3.75-3.90 (br, 1H), 3.91-4.06 (br, 1H), 4.55-4.78 (br, 1H), 5.05-5.46 (br, 3H), 5.81-6.15 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm):

δ 22.93, 26.11, 27.44, 28.55, 28.67, 29.41, 29.89, 32.09, 32.83, 35.42, 40.11, 29.54, 54.86, 79.31, 80.11, 130.57, 156.06, 156.37, 171.77.

Characterization of 12c. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.96-1.71 (br, 37H), 1.73-2.05 (br, 5H), 3.01-3.23 (br, 2H), 3.72-3.93 (br, 1H), 3.99-4.19 (br, 1H), 4.79-5.17 (br, 5H), 5.22-5.44 (br, 2H), 5.47-5.75 (br, 1H), 5.78-6.15 (br, 1H), 7.31 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.62, 26.12, 29(m), 32.38, 32.82, 35.30, 40.53, 49.67, 55.16, 66.84, 67.20, 128.27, 128.72, 130.57, 136.41, 156.84, 171.33. FTIR (KBr pellet, cm^{-1}): 3423, 3314, 3057, 2989, 2930, 2856, 1719, 1685, 1648, 1519, 1456, 1423, 1266, 1137, 1028, 973, 897, 742, 704.

Characterization of 12d. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.02-1.70 (br, 50H), 1.71-2.22 (m, 6H), 2.97-3.19 (br, 2H), 3.75-3.91 (br, 1H), 3.90-4.07 (br, 1H), 4.59-4.71 (br, 1H), 5.10-5.48 (br, 3H), 5.91-6.19 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.91, 26.09, 27.43, 28.53, 28.65, 29(m), 32.06, 32.11, 32.81, 35.43, 40.06, 49.54, 79.30, 80.09, 130.07, 130.52, 156.00, 156.36, 171.77. FTIR (KBr pellet, cm^{-1}): 3426, 3334, 3056, 2985, 2930, 2857, 1708, 1673, 1510, 1457, 1424, 1393, 1368, 1267, 1171, 1047, 1021, 971, 897, 864, 743, 705.

Characterization of 13. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.00-1.91 (br, 32H), 2.01-2.36 (br, 4H), 3.27-3.66 (m, 2H), 3.93-4.18 (br, 1H), 4.48-4.77 (br, 1H), 5.30 (s, br, 2H), 5.42 (s, br, 2H), 5.50-5.71 (br, 2H), 5.97-6.23 (br, 1H), 6.25-6.59 (br, 1H), 7.53 (s, br, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.09, 29(m), 32.87, 35.27, 49.97, 67.45, 69.81, 128(m), 130.57, 135.01, 136.28, 139.44, 169.28, 171.70. FTIR (KBr pellet, cm^{-1}): 3414, 2397, 3056, 2988, 2929, 2856, 1716, 1677, 1504, 1457, 1423, 1266, 1146, 1048, 971, 897, 740, 705.

Characterization of 14. ^{1}H NMR (300 MHz, DMSO-d$_6$, 140 °C, ppm): δ 0.78-0.98 (br, 6H), 1.13-1.54 (br, 33H), 2.83-2.11 (br, 4H), 2.31-2.46 (br, 2H), 3.20-3.38 (br, 2H), 3.57-3.81 (br, 1H), 4.06-4.23 (br, 1H), 5.04 (s, br, 2H), 5.27-5.47 (br, 2H), 6.46-6.66 (br, 1H), 7.01-7.13 (br, 1H), 7.33 (s, br, 5H). ^{13}C NMR (75 MHz, DMSO-d$_6$, ppm): No spectrum was obtained due to only partial solubility of the polymer in hot DMSO-d$_6$. FTIR (KBr pellet, cm^{-1}): 3575, 3506, 3300, 2975, 2856, 1726, 1654, 1535, 1460, 1365, 1241, 1070, 911.

Characterization of 15. ^{1}H NMR (300 MHz, CDCl$_3$, ppm): δ 0.75-1.02 (br, 12H), 1.03-1.77 (br, 47H), 1.84-2.06 (br, 4H), 3.73-3.91 (br, 1H), 3.98-4.24 (br, 1H), 4.28-4.53 (m, 1H), 4.98-5.53 (br, 3H), 6.08-6.58 (br, 2H), 6.66-7.14 (br, 1H). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): δ 18.15, 22.45, 23.08, 23.16, 24.98, 26.07, 27.04, 27.43, 28.53, 29(m), 30.54, 32.83, 35.14, 35.45, 41.25, 49.58, 52.27, 53.44, 80.27, 124.73, 125.74, 130.10, 130.55, 155.98, 171.39, 172.80. FTIR (KBr pellet, cm^{-1}): 3422, 2397, 3056, 2928, 2857, 1694, 1645, 1521, 1465, 1441, 1391, 1368, 1266, 1169, 1120, 1047, 1023, 970, 897, 874, 743, 706.

Results and Discussion

Monomer Synthesis

The synthesis of the amino acid and dipeptide branched dienes needed for this research is easily accomplished using standard peptide coupling chemistry to attach amino acid or peptide functionality to amine branched dienes. The amine branched dienes **3a** and **3b** were prepared in three steps giving an overall yield of up to 73% (Figure 3-1). The synthesis was achieved without strenuous purification of the intermediates — only simple acid/base extractions were performed. Alcohols **1a** and **1b** were prepared by the Grignard reaction of 5-bromo-1-pentene and 11-bromo-1-undecene, respectively, with ethyl formate.

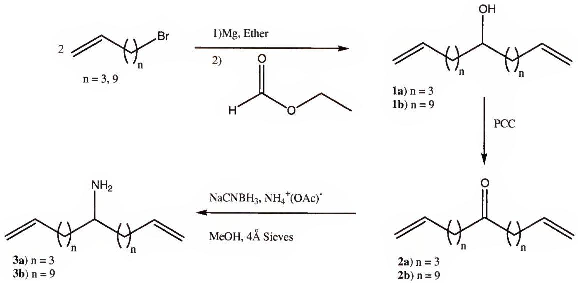


Figure 3-1. Synthesis of the amine branched dienes (**3a**) and (**3b**).

Oxidation of **1a** and **1b** with pyridinium-chlorochromate (PCC) gives the ketones **2a** and **2b**, respectively, in nearly quantitative yields. The ketones **2a** and **2b** can be subjected to reductive amination using ammonium acetate as the amine source, sodium cyanoborohydride as the reducing agent, and crushed molecular sieves, to help drive the reaction to completion, to give the crude amines **3a** and **3b**. Purification by flash chromatography using a 3:1:1 ethyl acetate:hexanes:methanol mobile phase yielded the pure amines. However, an alternative and faster purification was achieved by placing the crude amine on a silica gel plug (2 inches deep by 2½ inches wide), followed by successive washing with 3:1 hexane:ethyl acetate until no starting materials were detected by TLC. Methanol was then used to remove the pure amines **3a** and **3b** from the silica gel. ^{1}H NMR, ^{13}C NMR, and IR were used for structure characterization. This quick purification technique was possible because of the vast differences in polarity between the starting materials and the final product. Similar yields were achieved for both methods; however, lower yields were achieved for **3b** than for **3a**, which could be attributed to steric effects during the actual reactions, *i.e.* longer reaction times and/or more stringent conditions may be necessary to drive up the yields.

The amine **3c** was not synthesized by the method described for **3a** and **3b**, due to the lack of readily available starting material 10-bromo-1-decene. Alternative syntheses of the ketone **2c** have been published by Watson *et al.*[151] and Zantour *et al.*,[169] which use the inexpensive starting material 10-undecenoic acid, a fatty acid derivative. Watson's method involves the Claisen condensation reaction of ethyl 10-undecenoate, followed by dealkoxycarbonylation to give **2c** in low yields with difficult purification.[151] In Zantour's method, 10-undecenoyl chloride is reacted with 1.8 equivalents of triethylamine to form a ketene, followed by the ketene-ketene coupling reaction to form the intermediate β-lactone (Figure 3-2). Refluxing the intermediate in a sodium hydroxide solution opens the lactone, allowing decarboxylation to occur forming the ketone **2c** in high yields (82 %) with easy purification (Figure 3-2).[169] The ketone **2c** is then converted to the amine **3c** using the same methodology employed for the synthesis of amines **3a** and **3b** for an overall yield of 52 %.

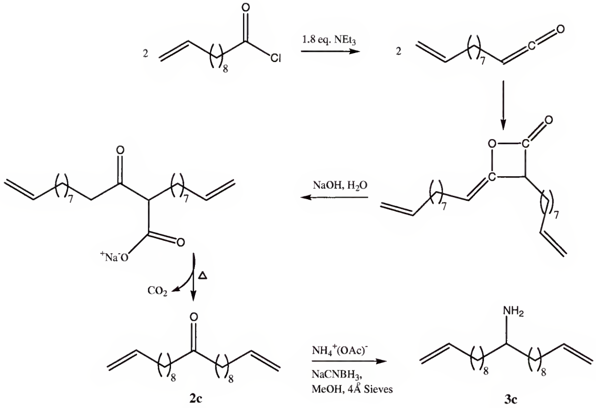
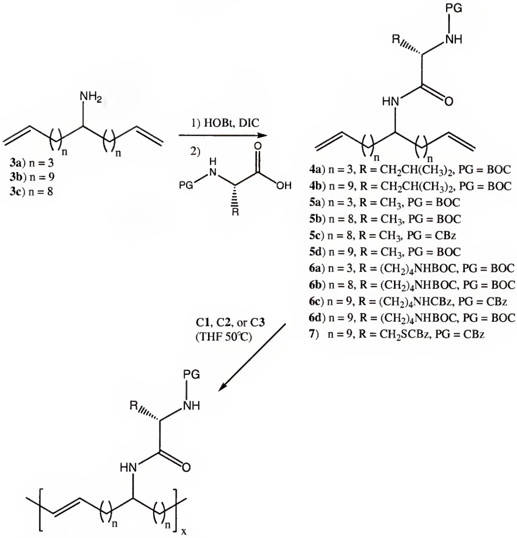


Figure 3-2. Previously published mechanism of ketone (**2c**) and synthesis of the amine branched diene (**3c**).

All of the amino acid branched dienes were prepared using simple textbook peptide coupling chemistry (Figure 3-3). The 3-spacer BOC-L-leucine branched diene (**4a**), the 3-spacer BOC-L-alanine branched diene (**5a**), and 3-spacer Di-BOC-L-Lysine (**6a**) were synthesized by coupling **3a** with the corresponding BOC protected amino acids using the standard peptide coupling method with 1-hydroxy benzatriazole (HOBt) as the catalyst and 1,3-diisopropylcarbodiimide (DIC), which was chosen due to its liquid nature that made it easy to handle, as the coupling reagent. Purification was achieved by 3 successive recrystallizations from CH_3OH/water yielding the pure products **4a**, **5a**, and **6a** in 78, 76, and 55 %, respectively.



3a) n = 3
3b) n = 9
3c) n = 8

4a) n = 3, R = $CH_2CH(CH_3)_2$, PG = BOC
4b) n = 9, R = $CH_2CH(CH_3)_2$, PG = BOC
5a) n = 3, R = CH_3, PG = BOC
5b) n = 8, R = CH_3, PG = BOC
5c) n = 8, R = CH_3, PG = CBz
5d) n = 9, R = CH_3, PG = BOC
6a) n = 3, R = $(CH_2)_4NHBOC$, PG = BOC
6b) n = 8, R = $(CH_2)_4NHBOC$, PG = BOC
6c) n = 9, R = $(CH_2)_4NHCBz$, PG = CBz
6d) n = 9, R = $(CH_2)_4NHBOC$, PG = BOC
7) n = 9, R = CH_2SCBz, PG = CBz

10a) n = 3, R = $CH_2CH(CH_3)_2$, PG = BOC
10b) n = 9, R = $CH_2CH(CH_3)_2$, PG = BOC
11a) n = 3, R = CH_3, PG = BOC
11b) n = 8, R = CH_3, PG = BOC
11c) n = 8, R = CH_3, PG = CBz
11d) n = 9, R = CH_3, PG = BOC
12a) n = 3, R = $(CH_2)_4NHBOC$, PG = BOC
12b) n = 8, R = $(CH_2)_4NHBOC$, PG = BOC
12c) n = 9, R = $(CH_2)_4NHCBz$, PG = CBz
12d) n = 9, R = $(CH_2)_4NHBOC$, PG = BOC
13) n = 9, R = CH_2SCBz, PG = CBz

Figure 3-3. Synthesis and polymerization of the amino acid branched dienes.

The 9-spacer di-CBz-L-lysine branched diene (**6c**) and the 9-spacer di-CBz-L-cysteine branched diene (**7**) were prepared by coupling **3b** with the corresponding CBz protected amino acid using the HOBt/DIC method and purified by the recrystallization method described above to yield **6** in 47 % and **7** in 29 %. The 9-spacer BOC-L-alanine branched diene (**5b**), 9-spacer BOC-L-leucine branched diene (**4b**), and 9-spacer BOC-L-lysine branched diene (**6b**) were prepared by coupling the BOC protected amino acids with **3b** using the HOBt/DIC method and purified as described above to give the pure dienes in 22 % yield for **5d,** 39 % yield for **4b**, and 87 % yield for **6b**. The BOC and CBz protected 8-spacer L-alanine branched dienes (**5b** and **5c**) were prepared by reacting the corresponding protected amino acids with **3c** using the above methodology to yield the pure monomers **5b** and **5c** in 75 % and 74 % yields, respectively. Likewise, the 8-spacer di-BOC-L-lysine branched polymer was prepared by coupling di-BOC-L-lysine with **3c** to afford the desired monomer in 73 % yield. Further, the dipeptide branched dienes **8** and **9** were easily prepared by coupling the protected dipeptides with **3b** using the HOBt/DIC coupling method and purified as described above in 46 % and 95 % yield for **8** and **9,** respectively (Figure 3-4).

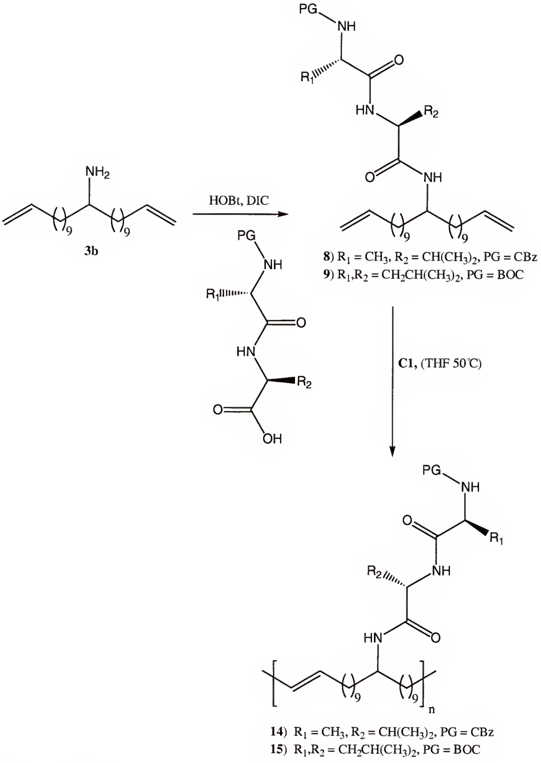

3b
HOBt, DIC
C1, (THF 50℃)
8) $R_1 = CH_3$, $R_2 = CH(CH_3)_2$, PG = CBz
9) $R_1,R_2 = CH_2CH(CH_3)_2$, PG = BOC
14) $R_1 = CH_3$, $R_2 = CH(CH_3)_2$, PG = CBz
15) $R_1,R_2 = CH_2CH(CH_3)_2$, PG = BOC

Figure 3-4. Synthesis and polymerization of the dipeptide branched dienes.

Some observations were made during the synthesis of the monomers. It appears that a longer reaction time (up to 48 hours for the protected dipeptides), performing the reaction in refluxing THF, and using 2.5 equivalents HOBt gave the best reaction yields. Also, CH_2Cl_2, $CHCl_3$, and THF were used as solvents for the amino acid synthesis, but the latter was used preferably due to the ease of availability of the pure dry solvent in our laboratory, the high yields obtained, and the increased solubility of the HOBt and amino acids/dipeptides in this solvent. Purification was best achieved by filtration of the insoluble urea and evaporation of the solvent, followed by 3 recrystallizations from ethanol/water or methanol/water depending on the melting point of the monomers, *i.e.* ethanol/water was used for high melting monomers and methanol/water was used for low melting monomers. It was found that 3 recrystallizations resulted in pure compounds by thin layer chromatography (TLC), elemental analysis, NMR (^1H and ^{13}C), and HRMS; moreover, the yields were improved if extractions were not performed to remove the HOBt and soluble urea due to emulsions that formed during the extraction process.

Polymer Synthesis

ADMET is a simple condensation polymerization that allows for precise branch and/or functionality placement along the polymer backbone as determined by monomer design. ADMET is commonly performed in the bulk; however, since the monomers were all solids, solution polymerization was used requiring a small quantity of solvent (~1 mL) with an argon purge to aid in the removal of ethylene (Figure 3-5).

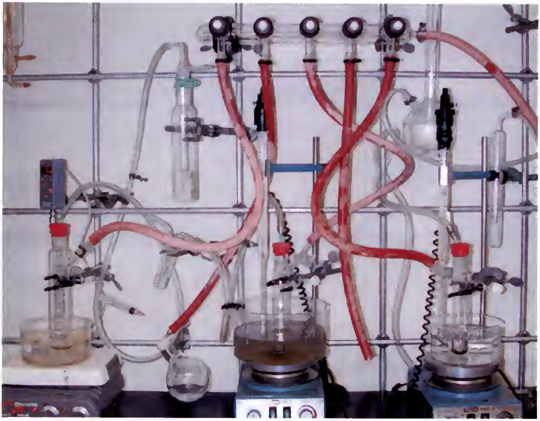
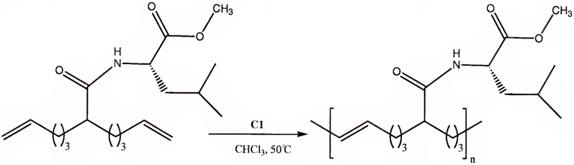


Figure 3-5. Three solution-based ADMET reactions in progress.



16

Figure 3-6. The first bio-olefin (**16**) prepared by ADMET.[148,150]

The first bio-olefin prepared was polymer **16** with a branch on every 9th carbon. This polymer was a high melting polymer that was polymerized easily using catalyst **C1** (Figure 3-7) in $CHCl_3$ (this polymer will be discussed in detail in Chapter 4) (Figure 3-6). However, when applying this polymerization methodology towards the preparation of *C*-terminus bio-olefins an interesting occurrence was observed. Most of the monomers were not polymerizable using catalyst **C1** in $CHCl_3$. There appears to be a solvent effect associated with this chemistry. For instance, when monomer **6c** was polymerized using $CHCl_3$ as the solvent only oligomeric products were observed, whereas the monomer was successfully polymerized to **12c** ($\overline{M}_n$ of 25,000 g/mol) using THF as the solvent (Table 3-1) — a similar observation was observed for most of the monomers. The low conversion in $CHCl_3$ is likely due to complexation of the catalyst to the amino acid functionality of the dienes;[148,150,159-163] therefore, THF, a labile ligand, appears to break up complexation, freeing the catalyst for metathesis. This is the first known example of THF being used as a solvent for ADMET polymerization. As shown in Table 1, monomers **4b**, **5b**, **5c**, **5d**, **6b**, **6c,** and **6d** were successfully polymerized using catalyst **C1** with THF as the solvent to form polymers **10b**, **11b**, **11c**, **11d**, **12b**, **12c**, and **12d** with $\overline{M}_n$s equal to 20,000, 37,000, 21,000, 13,000, 20,000, 25,000, and 11,000, respectively (Table 4-1). Further, no terminal olefins resonances were observed in the ^{1}H NMR for these polymers, which is a phenomenon observed for high molecular weight ADMET polymers.

Monomers **4a**, **5a**, and **6a** with 3 methylene spacers between the olefin and the amino acid branch were synthesized to compare the corresponding polymers with polymer **16**. However, the polymerization of **4a** in THF and **5a** in THF or $CHCl_3$ with catalyst **C1** resulted in only oligomer formation in all cases. One major difference is evident when comparing these monomers; the location of the amine and carbonyl group relative to the diene. We reported previously that the amide carbonyl prevented or limited the polymerization of linear amino alcohol containing dienes when located two or three carbons from the olefin, due to intermolecular complexation of the nucleophilic amide carbonyl with the catalyst.[148-150] In this case, we believe the molecular orientation of monomers **4a** and **5a** also allows for complexation to occur between the monomer functionality and catalyst resulting in only oligomer formation and one possible example of this complexation is demonstrated in Figure 3-7.

Polymer	$\overline{M}_n$ ^{a}**(g/mol)**	**PDI^a**	T_m ^{b}**(°C)**	T_g ^{b}**(°C)**
10b	20,000	1.96	C	34
11b	37,000	1.85	C	7
11c	21,000	1.89	46^e	D
11d	13,000	2.11	C	18
12b	20,000	1.76	64^e/48^f	D
12c	25,000	1.92	96	D
12d	11,000	1.92	60	D
13	14,000	1.76	110	D
14	12,000	2.61	150	D
15	6,500	1.66	C	40

Table 3-1. The GPC and DSC data for the "*C*-terminus" polymers. a)values were calculated by GPC versus polystyrene standards. b) Data obtained using a Perkin Elmer DSC 7. c) No T_m observed over the scanned range of -80 °C to 190 °C. d) No T_g observed over the scanned range of -80 °C to 190 °C. e) The T_m reported is that of the solvent crystallized sample; no T_m was observed from the melt crystallized sample. f) T_m from the melt crystallized sample.

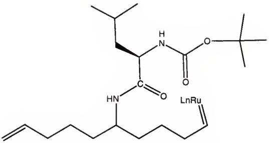
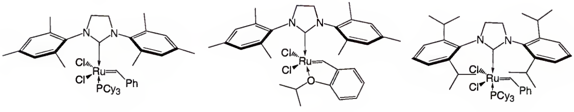


Figure 3-7. A possible complexation between the amide carbonyl functionality and monomer **4a** when polymerized with catalyst **C1**.

New developments in metathesis catalysts have resulted in more active and more functional group tolerant catalytic species, which show high activities even at low temperatures. Recent work in our group has demonstrated that catalyst **C3** (Figure 3-8) is much faster than **C1** for the polymerization of 1,9-decadiene, whereas catalyst **C2** (Figure 3-8) demonstrated a higher activity in the presence of polar functionality than **C1**. Therefore, these highly active catalysts were used to try to polymerize monomers **4a**, **5a**, and **6a** and the results of this study are given in Table 3-2. The results for **10a** and **10b** suggest that catalyst **C2**, which has been shown to need a functional group such as an ether group (THF) to maintain its activity, may be stabilized by the functionality of the monomer rather than rendered inactive.[173] However, ^{1}H NMR and ^{13}C NMR gave interesting results for polymer **10a**: extra peaks were observed at 5.55-5.72 ppm and 124 ppm for ^{1}H and ^{13}C NMR, respectively, which are not observed for **11a**. These can not be explained by external olefins. It is possible that they result from isomerization and/or the secondary structure of the polymer, where the functional groups are in close proximity to the olefinic or amide protons causing a downfield shift. The results for polymer **12a** are opposite of **10a** and **11a**, leaving the explanation for this observed activity, or lack there of, unknown at this time. Further, in all cases, catalyst **C3** produces polymers with molecular weights between that obtained by **C1** and **C2**. Even though there are no explanations to why variation of 2nd generation Grubbs' type metathesis catalysts yield different results, a positive outlook towards future applications of this methodology is that if one metathesis catalyst does not polymerize a given monomer another variation might.



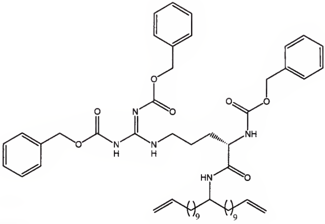
C1 **C2** **C3**

Figure 3-8. The three catalysts used in this work. **C1** is the Grubbs' 2nd generation catalyst, **C2** is the Hoveyda version of **C1**, and **C3** is the Mol derivative of **C1**.

Polymer	$\overline{M}_n$[a](g/mol) **C1**	$\overline{M}_n$[a](g/mol) **C2**	$\overline{M}_n$[a](g/mol) **C3**	**PDI**[a] **C1/C2/C3**
10a	trimer[b]	13,000	c	NA/1.34/NA
11a	Dimer[b]	12,000	8,000	NA/1.50/1.34
12a	37,000	14,000	26,000	1.63/1.59/1.49

Table 3-2. Comparison of the molecular weights obtained for **10a, 11a**, and **12a** using catalysts **C1**, **C2**, and **C3**. a) $\overline{M}_n$ and PDI were calculated by GPC relative to polystyrene standards. b) Calculated by end group analysis by ^{1}H NMR. c) No data was collected with this catalyst. NA) Not Available.

To test the limitations of this methodology towards the polymerization of highly polar dienes, monomer **7** bearing a cysteine branch, which has a CBz protected sulfur — a functional group never before polymerized by ADMET — was synthesized. This amino acid was of particular interest, since the unprotected sulfur could be used to make crosslinked materials that could have potential for uses such as hydrogels.[131] The monomer was successfully polymerized to yield **13** with a $\overline{M}_n$ of 14,000 g/mol. In addition to the cysteine branched monomer, we were interested in an arginine branched (Figure 3-9), since it possesses the highly polar functional group guanidine. Also arginine is found in the biologically active peptide sequence RGD (arginine-glycine-aspartic acid), which is a target for this research. Thus, before synthesizing an RGD branched monomer, it had to be determined if the guanidine group was polymerizable. Unfortunately, monomer **17** suffered from slow reaction kinetics; the best molecular weight obtained was 5,000 g/mol, which corresponds to a DP of around 7. In all cases external olefins were observed in the ^{1}H NMR, further supportive of a slow rate of metathesis.



17

Figure 3-9. Tri-CBz Arginine monomer that was not capable of being polymerized to high polymer.

The successful polymerization of dipeptide branched monomers will lead towards the synthesis of monomers bearing longer peptides, which could have specific biological properties. Therefore, we attempted to polymerize the dipeptide monomer **8** to polymer **14** using THF as the solvent. The polymer was relatively insoluble in THF; however, by stirring 10 mg of polymer in 2 ml of THF overnight, enough polymer was dissolved at a high enough concentration to allow for successful GPC molecular weight determination

(12,000 g/mol). Also, the polymerization of the dipeptide monomer **9** yielded **15**, which was shown to be a high polymer by the lack of terminal olefin resonances in ^{1}H NMR spectrum, and had a GPC molecular weight of 7,500 g/mol relative to polystyrene. Polymer **15** could not be purified by precipitation in cold methanol, since it was slightly soluble and could not be precipitated even with the addition of water. Thus, the purification was achieved using a procedure by Maynard and Grubbs, which was modified by Dr. Richard Pederson of Materia, Inc. The dissolution of the polymer in CH_2Cl_2 followed by the addition of 25 equivalents of 1$\underline{M}$ tris(hydroxymethyl)phophine (THP) in isopropyl alcohol made a water soluble, extractable catalyst residue allowing for easy purification.[174]

Hydrogenation and Deprotection of Bio-olefins

To use bio-olefins for material applications, it will be necessary to saturate the backbone olefinic as well as to deprotect the amine functionality. Only initial work has been done in this area due to the rather insoluble characteristics of both the saturated and deprotected polymers. Polymers **10b**, **11b**, **12b**, and **12c** were used for hydrogenation and deprotection study. Polymers **10b** and **11b** were hydrogenated using Pd(C) (5 mol %) in THF/ethyl acetate at 400 PSI H_2 in a Parr Bomb submerged in an 80 °C oil bath. The hydrogenations were successful (~95 %) by ^{1}H NMR, although a lack of solubility made thorough analysis difficult. Further, isolation of the bio-olefins from the activated carbon proved very challenging and required the carbon to be stirred in boiling THF and filtered three times. The polymers were then stirred in concentrated trifluoroacetic acid (TFA) for 12 hours, and after 4 hours the polymers began to precipitate out of solution. Purification of **10b** was achieved by washing the polymer with sodium hydroxide (6$\underline{M}$) to yield the neutral ethyl acetate soluble polymer, followed by solvent-casting on a Teflon^{TM} plate. However, once the polymer film had dried, it was completely insoluble in all solvents even acids. Deprotected polymer **11b** was insoluble in everything and was therefore purified by washing the insoluble polymer with NaOH (6M), D.I. water, and drying under vacuum (10^{-2} mmHg). Both were analyzed by IR to verify that the amide C=O was no longer observed, which indicated successful deprotection.

The CBz protecting group was chosen, since it can be removed under standard hydrogenation conditions using Pd(C). Thus, polymer **12c** was protected with CBz groups so that hydrogenation and deprotection could be performed in a one step reaction. But after 72 hours of hydrogenation using the methodology applied above, only the backbone was hydrogenated — the protecting group remained untouched. A variety of harsher hydrogenation conditions were employed, *i.e.* higher temperatures (>100 °C) and high pressures (600 PSI H_2); once again, only the backbone was hydrogenated not the CBz group. The use of Pearlman's catalyst was investigated, since it is well known for the removal of benzyl groups; however, these conditions were still incapable of removing the CBz groups from bio-olefins. Other methods attempted included the use of formic acid/Pd(OH) hydrogen transfer type of hydrogenation/deprotection, but again the CBz group remained untouched. Thus, when applying this methodology to polymers intended for deprotection, more labile protecting groups must be used, *e.g.* BOC.

As mentioned above, bio-olefins are hard to remove from activated carbon; therefore, polymer **12b** was hydrogenated using Wilkinson's heterogeneous catalyst (5 mol %). The hydrogenation was run at 600 PSI at 100 °C for 3 days in a THF/ethyl acetate solvent mixture. The polymer was precipitated in acidic methanol, which initially yielded a white precipitate but formed a brown aggregate upon filtration. The brown color was a result of catalyst residue. ^{1}H NMR in THF revealed the hydrogenation had gone to approximately 95 % completion, but this reaction was not optimized, *i.e.* higher pressures and temperatures would probably push the reaction to completion. Deprotection has not been attempted on this polymer.

Thermal Characterization

Differential scanning calorimetry (DSC) measurements were completed to determine if the samples were completely amorphous or semicrystalline in nature. The study of semicrystallinity is important due to the inherent strength provided by the crystalline regions of a polymer. Analysis of the bio-olefins with a branch on every 9th carbon of the backbone was not very informative. Polymers **11a** and **12a** did not show a T_g or a T_m over the scanned range of -80 °C to 180 °C, probably due to the inability to load enough sample into the DSC pan; however, polymer **10a** exhibited a T_m at 59 °C, but only on the first DSC scan, *i.e.* from solvent evaporation and not from the melt.

The BOC protected polymers **10b**, **11b**, and **11d** are amorphous with glass transitions (T_g) at 34 °C, 7 °C, and 18 °C respectively, where the lack of crystallinity likely is due to the presence of the bulky BOC protecting groups. Polymers **11c** and **12c** each possess CBz protecting groups resulting in semicrystalline materials with melting points of 46 °C and 96 °C, respectively. Surprisingly, polymer **12d**, which has two BOC protecting groups per repeat unit, also is semicrystalline with a T_m of 60 °C. Why is polymer **12d** semicrystalline? We expected an amorphous polymer, as is the case for the analogous polymers **10b**, **11b**, and **11d**. The presence of two "greasy" BOC protecting groups per repeat unit in **12d** should inhibit crystallization. This unexpected crystallinity could be explained by the added polarity of the amino acid branch in polymer **12d**, which has two hydrogen bonding sites per repeat unit. Figure 3-10 compares the DSC spectra for polymers **12a** and **12d**, which differ only in protecting group strategy. These DSC spectra demonstrate that although the BOC protecting groups do not prevent crystallization, they do affect the thermal properties of the resulting polymers. Further, polymer **12b** which has two less carbons between branches than **12d** is also semicrystalline with a similar T_m (64 °C) from the solvent evaporated sample and 48 °C from the melt-crystallized sample. The possibility that polarity of the side branch has an impact on the semicrystalline nature of the polymer is further supported by the analysis of the cysteine branched polymer **13**, which is semicrystalline with a T_m of 110 °C.

The dipeptide branched polymers **14** and **15**, having a CBz protected alanine-valine branch and a BOC protected leucine-leucine branch, respectively, were also analyzed. Polymer **14** is semicrystalline with a T_m value of 150 °C (Figure 3-11), whereas polymer **15** is amorphous with a T_g of 40 °C. Interestingly, the T_g found for polymer **15** is similar to that found for the single BOC protected leucine branched polymer **10b**. The differences in semicrystallinity can be explained not only by the difference in protecting groups, but by the relatively small alkyl branches, methyl and isopropyl, on the dipeptide of polymer **14**, which should have a smaller effect on the crystallization than the two isobutyl branches on the leucine moieties of polymer **15**.

As is evident by the DSC study, both the nature of the protecting group and the polarity of the amino acid or peptide functionality appear to influence the crystallinity and the T_m of the resulting polymers. The differences in the percentage of mass composition of the amino acid versus polymer backbone, as well as the high T_m values obtained for some of the polymers, demonstrate that it is indeed the amino acid or peptide functionality that is responsible for the semicrystallinity we observe. Further, hydrogenation of the backbone did not change the T_m of polymer **12b**, which also supports this concept.

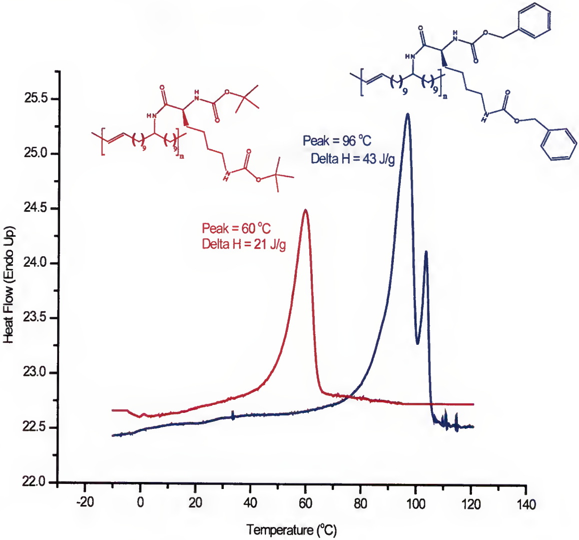


Figure 3-10. Comparison of the melt transitions of polymers **12a** and **12b**.

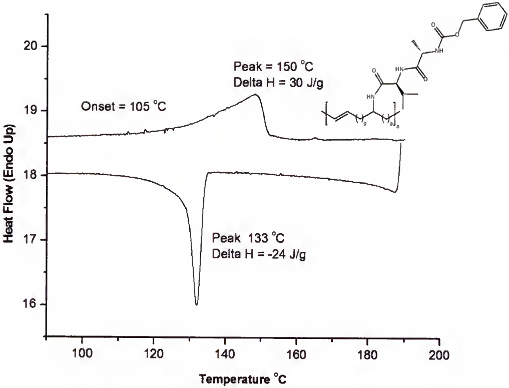


Figure 3-11. The DSC trace of polymer **14**.

Initial WAXD and SAXD Results

The crystalline nature described above causes a very important question to be asked; what is responsible for the crystalline regions? As suggested above, a comparison of the trends observed from the DSC data of the polymers suggests that the amino acid/dipeptides may be responsible for this semicrystallinity. However, polyethylene is known to be the most crystalline polymer and usually dominates the crystalline regions of copolymers,[175] so to suggest that the amino acid branch of these bio-olefins is responsible for this phenomenon, goes against common scientific thought and literature in this area.

To help answer this important question, we have begun collaboration with Dr. Kim Chaffin and Dr. Frank Bates at the University of Minnesota. The data given is not complete, and thus no concrete conclusions can be made at this point, but some trends can be observed. The CBz-alanine polymer (**11c**), lysine polymers (**12b**, **12c**, and **12d**), the di-CBz-cysteine polymer (**13**), and the hydrogenated 8-spacer-di-BOC lysine polymer (**$H_2$12b**) were analyzed by wide angle x-ray diffraction (WAXD) (Figure 3-12) and small angle x-ray diffraction (SAXD) (Figure 3-13).

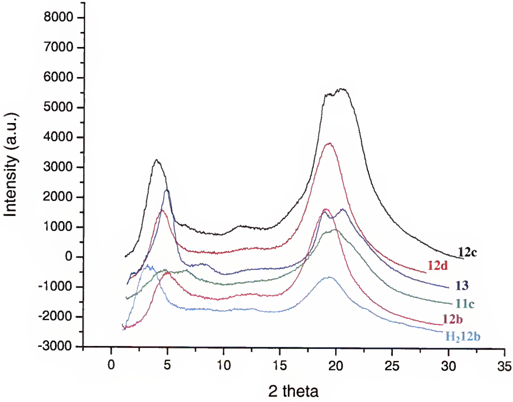


Figure 3-12. The WAXD scattering on the alanine, lysine, and cysteine branched polymers.

As can be see in Figure 3-12, the alanine-branched polymer **11c**, which has the smallest side branch of the chiral amino acids (methyl), appears to set the WAXD scattering pattern observed for the other monomers. Further, calculations from the WAXD scattering give percent crystallinities of around 60 %, which if true may let these bio-olefins be spun into fibers. An analysis of the SAXD scattering (Figure 3-13) shows that theses bio-olefins have no long range ordering indicating no lamellae formation, which is also supportive of our suggestion that the amino acids are responsible for the semicrystallinity. Spectral comparisons between WAXD and SAXD for each monomer analyzed along with the calculated d-values are given in Appendix 1.

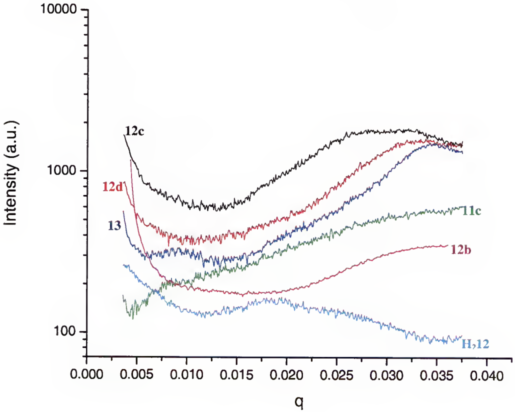


Figure 3-13. The SAXD scattering of the alanine, lysine, and cysteine branched polymers.

Initial Surface Examination

Bio-olefins bearing peptide branches could prove useful for a variety of biologically active applications. Since branches can be incorporated on the surface of a polymer film or within a polymer film, the question had to be asked: are the peptides located on the surface of the polymer film? To answer this question, collaboration was started with Prof. Shunsaku Kimura and Mr. Shigekatsu Fujii at Kyoto University in Kyoto, Japan. They used the relatively new surface analysis method, polarization modulation infrared reflective absorption spectroscopy (PM-IRRAS),[176-180] to analyze a bio-olefin monolayer, which was prepared in a Langmuir trough (Figure 3-14**a**). Figure 3-15 shows the surface pressure isotherms of the bio-olefins **14** (red) and **15** (green) taken during the monolayer film formation. The schematic in Figure 3-14**b** demonstrates the method at which the IR measurements were taken on the monolayers, where s is the phase shift of the perpendicular component and p is the phase shift of the parallel component.[181] Figure 3-14**c** demonstrates the two vibrational frequencies measured; Amide 1 is the CO stretch and amide 2 is the CN stretch. A ratio of the two stretches can give the orientation of the dipeptide branches (Figure 3-16): if amide 1 is the stronger stretch the CO bond is located perpendicular to the surface, and if amide 2 is stronger the CN bond is located perpendicular to the surface. Therefore, the ratio suggests that polymer **14** with the less bulky side groups is positioned at approximately 45° from the polymer surface, whereas the bulky dipeptide-branched polymer **15** sits perpendicular to the polymer film (Figure 3-17).

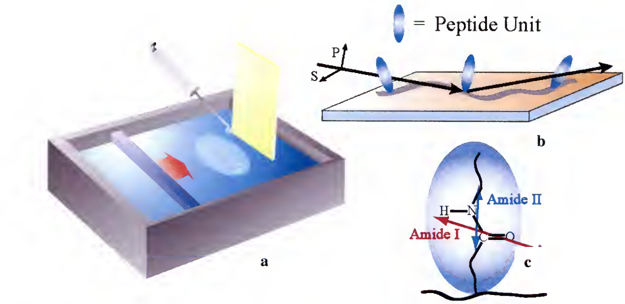


Figure 3-14. Surface analysis experiment using PM-IRRAS of a bio-olefin monolayer. a) Diagram of the preparation of the monolayer film on a Langmuir trough. b) Demonstration of polarization modulation infrared reflective absorption spectroscopy (PM-IRRAS). c) Demonstrations of the monitored amide I and amide II vibrations.

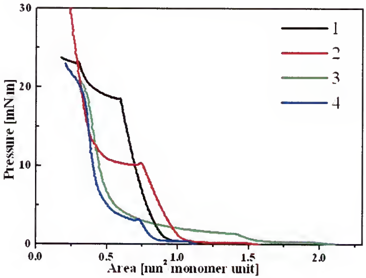
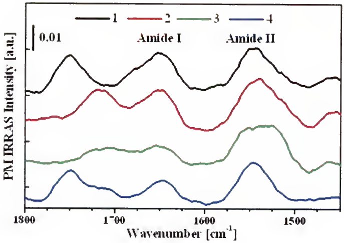


Figure 3-15. Surface pressure isotherm of dipeptide branched bio-olefins. Red is the CBz-alanine-valine branched polymer (**14**) and green is the BOC-leucine-leucine branched polymer (**15**). Also pictured Black and Blue are *N*-terminus bio-olefins that will be discussed in CH. 4.



Ratio of Amide I/Amide II
14: 0.73 15: 0.48

Figure 3-16. The PM-IRRAS spectrum of polymers **14** (red) and **15** (green). Also pictured are the *N*-terminus bio-olefins (black and blue) that will be discussed in CH. 4.

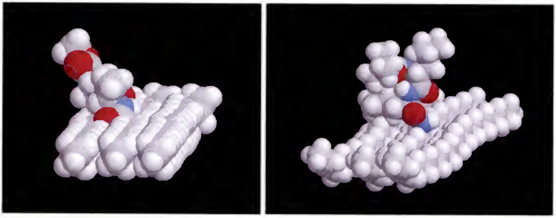


Figure 3-17. Three-dimensional illustrations of the dipeptide branched polymers. Left) 3D picture of what polymer **14** looks like with the dipeptide ~45 ° from the polymer surface. Right) 3D picture of the monolayer of polymer **15**, demonstrating that the dipeptide is located approximately perpendicular to the polymer surface.

Initial Instron Results

Although many of the bio-olefins described in this chapter form apparently strong films, only one has been tested thus far for tensile strength and modulus through collaboration with Professor Anthony Brennan and Mr. Clay Bohn. The Instron data for polymer **11c** is shown in Figure 3-18 as a stress/strain curve, which demonstrates a modulus of 222 MPa, which is in the same range as low density polyethylene (LDPE),[182] with a strain at break of 263 %. This result demonstrates the good physical properties than can be obtained with only moderate molecular weights.

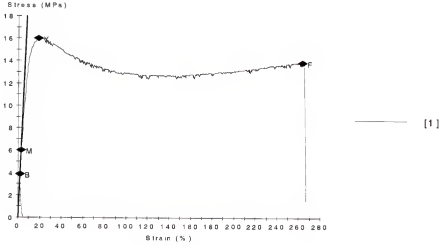


Figure 3-18. Stress/strain curve for polymer **11c**.

Conclusions

"*C*-terminus" bio-olefins have been prepared using ADMET polycondensation from monomers synthesized in high yields using simple peptide coupling chemistry. The resulting polymers have T_m values of up to 150 °C with up to 60 % crystallinity, which could lend them useful for possible biomedical applications and this semicrystallinity appears to be due to the amino acid or peptide functionality and not the polyolefin backbone, as determined by DSC comparisons and the initial WAXD and SAXD data. Also, the polarity of the amino acid or peptide branch appears to greatly affect the crystallinity of the sample as well as the T_m values; the higher the polarity of the amino acid or peptide branch the higher the crystallinity and the higher the T_m. In addition, initial surface studies reveal that the dipeptide branched polymers are aligned on the surface, a property that could lend these very useful for biomaterial applications such as cell binding.

We believe the ability to use ADMET to polymerize amino acid and peptide containing monomers could lead towards the synthesis of designer biomaterials for specific biological applications. This methodology has the advantage that the amount of functionality as well as the placement of the branch can be completely controlled by either monomer synthesis or simple copolymerization.

CHAPTER 4
"*N*-TERMINUS" ADMET BIO-OLEFINS

Introduction

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As discussed in the previous chapters, the incorporation of amino acid functionality and chirality into a polymer's repeat unit can increase the solubility of the material that results, in addition to enhancing the potential to form secondary structures such as α-helices and β-sheets.[4,125] Such polymers can be useful as drug-delivery agents, chiral recognition stationary phases, asymmetric catalysts, metal ion absorbents, and biocompatible materials.[4,113,114] In addition, advancements in chiral separation and monomer synthesis have led to a wide availability of inexpensive and enantiopure protected amino acids; the field is ripe for exploration.

For example, Endo and coworkers synthesized a variety of amino acid and peptide branched acrylamides via radical polymerizations,[120,123,124,129,130,164] North *et al.*[132-135] have prepared polyacrylates where the amino acid is attached through the alcohol side chain of a serine moiety leaving the *N* and *C*-terminus of the amino acid available for further chemistry, and Ayres and coworkers have prepared elastin-based polyolefins via a "living" polymerization technique, atom transfer radical polymerization (ATRP).[183] The subject has even evolved to polymers based on conjugated systems; a variety of amino acid branched polyacetylenes have been synthesized.[184-186]

Given the breadth of application based on the metathesis reaction, it is not surprising to find that ring opening metathesis (ROMP) has been employed to prepare amino acid and peptide-branched polymers,[165-167] including the polymerization of norbornene functionalized with the biologically active tripeptide RGD (arginine-glycine-aspartic acid).[168] Copolymerization with penta(ethylene oxide) substituted norbornene yielded a water soluble polymer capable of inhibiting cell binding to fibronectin, a property which could be useful for a variety of biomedical applications.[165,166]

As demonstrated in chapters 1 and 2, acyclic diene metathesis (ADMET) chemistry also proves viable for the preparation of amino acid polymers.[136-138, 148,150,152,153,187-189] This chapter describes the synthesis and properties of polymers containing amino acid and dipeptide-branched polyolefins, termed bio-olefins, where the functionality is attached through the *N*-terminus rather than the *C*-terminus, polymers which offer the potential of having the carboxylic acid present on the surface of the material. Complete synthetic details and thermal analysis of these polymers are discussed. In addition, preliminary data on WAXD and SAXD diffraction, surface properties, tensile strengths, and the pursuit of a biologically active bio-olefin are discussed.

Experimental

Chemicals

Reagents and chemicals were purchased and used as received from the Aldrich chemical company, unless otherwise noted. Diethyl Ether and THF were used as received from Fisher Scientific unless dry solvents were required, which were obtained from the Aldrich keg system and dried over Al_2O_3. Methylene chloride, methanol, and chloroform were used as purchased from Fisher. Anhydrous DMF (99.8 %) was used as purchased in an Aldrich sure seal container equipped with an Aldrich Schlenk cap. The

2^{nd} generation Grubbs' Ru catalyst (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride) (**1**) was used exclusively and was synthesized as described previously by Grubbs *et al.*[157] The protected amino acids, peptides, and resins were used as purchased from Bachem, except for H-Leu-OMe, which was purchased from Sigma-Aldrich.

Instrumentation

All ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Associates Gemini 300, Varian Associates VXR 300, or a Varian Associates Mercury 300 spectrometer. All chemical shifts were referenced to TMS (0.00 ppm) for ^{1}H NMR and to $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.51 ppm) for ^{13}C NMR.

Gel permeation chromatography (GPC) of the unsaturated ADMET polymers was performed using a Waters Associates GPCV2000 liquid chromatography system with an internal differential refractive index detector (DRI), an internal differential viscosity detector (DP), and a Precision 2 angle light scattering detector (LS). The light scattering signal was collected at a 15 degree angle and corrected at a 90 degree angle. The three in-line detectors were operated in series in the order of LS-DRI-DP. The chromatography was performed at 45 °C using two Waters Styragel HR-5E columns (10 microns PD, 7.8 mm ID, 300 mm length) with HPLC grade THF as the mobile phase at a flow rate of 1.0 mL/min. Injections were made at 0.05-0.07 % w/v sample concentration using a 322.5 μL injection volume. The Precision LS was calibrated using a narrow polystyrene standard having a $\overline{M_w}$ = 65,000 g/mol.

Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC 7 at a heating rate of 10 °C/min using indium and p-nitrotoluene as calibration standards with heats of fusion referenced against indium. The samples were scanned three times to remove recrystallization differences between samples and when possible the results reported came from the third scan. The results are listed in tabular form (Table 1) as well as within the text as T_m (melting peak) and T_g (glass transition at ½ C_p).

Initial stress/strain data was collected on an Instron model 1122 load frame upgraded with an MTS ReNew system running MTS TestWorks 4 software. The tests reported herein were performed using an Instron 500 g load cell.

Characterization

Strenuous purification was only performed on the final monomers reported herein. Only ^{1}H NMR and ^{13}C NMR spectra are reported for the premonomers (**2**-**6**). All of the monomers were fully characterized by ^{1}H NMR, ^{13}C NMR, EI/HRMS, and elemental analysis with purity confirmed by TLC. The polymers were characterized by ^{1}H NMR, ^{13}C NMR, GPC, and DSC.

Monomer Synthesis

The synthesis of 2-but-3-enylhept-6-enoic acid (2). A lithium diisopropyl amide (LDA) solution was prepared by adding n-BuLi (34.6 mL, 0.0864 mol) drop-wise to a stirred solution of THF (50 mL) and dry, distilled diisopropyl amine (11.93mL, 0.0864 mol) at 20 °C in a 250 ml round bottom flask equipped with an addition funnel under an Ar purge. The reaction mixture was cooled to 0 °C by submersion into an ice bath, followed by the addition of 5-hexenoic acid (4.042 g, 0.0388 mol) dropwise. After the addition of 5-hexenoic acid was completed, hexamethylphosphoramide (HMPA) (7.89 g, 0.0441 mol) was added, and the solution was gradually warmed to room temperature for 1 hour, followed by 2 hours at 50 °C. After heating, the solution had turned from a dark yellow to a dark purple. The solution was subsequently cooled to –78 °C by submerging the reaction vessel into an isopropanol/CO_2 bath, and 5-bromopentene was added dropwise. The solution was warmed to room temperature and stirred for 14 hours, heated for 1 hour at 40 °C, and finally cooled to room temperature preceding final reaction workup. D.I. H_2O (30 mL) was added to the mixture and the solution was acidified with 1M HCl followed by extraction with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with 10% HCl (2 x 20 ml) followed by saturated NaCl (2 x 20 mL), and concentrated via rotary evaporation. The crude product (5.70 g) was dried over $MgSO_4$, filtered by Büchner filtration, and further purified by column chromatography using a 3:1 hexane:ethyl acetate solution. This yielded the pure 2-but-3-enylhept-6-enoic acid (2) (1.20 g, 16 %) as verified by GC and NMR. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.31-1.78 (m, 6H), 1.99-2.15 (m, 4H), 2.31-2.46 (m, 1H), 4.89-5.06 (m, 4H), 5.69-5.87 (m, 2H) 11.16-11.92 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.44, 31.12, 31.40, 31.43, 33.54, 44.68, 114.79, 115.25, 137.66, 138.30, 182.85.

Synthesis of 2-pent-4-enyl-hept-6-enoic acid (3). To a 500 mL three neck round bottom flask equipped with a stir bar, reflux condenser, and addition funnel was added diethyl malonate (12.01 g, 75.0 mmol, 11.3 mL) dropwise to a slurry of NaH (10.00 g, 60 % in mineral oil, 0.250 mol) in THF (30.0 mL). 5-Bromo-1-pentene (25.00 g, 167.9 mmol) in THF (10.0 mL) was then added dropwise. The reaction was stirred at room temperature for 1 hour and at reflux for an additional 24 hours, and monitored by TLC using a 3:1 hexanes:ethyl acetate mobile phase. Additional 5-bromo-1-pentene (1.25 g, 8.4 mmol, 1.0 mL) and NaH (1.00 g, 60 % in mineral oil, 25.0 mmol) were added and the reaction was stirred under reflux. After 5 hours, the reaction appeared to be complete by

TLC. The mixture was then cooled in an ice bath, and water was added slowly to neutralize the remaining NaH. Then 50 mL water (total ~ 100 mL) and ethanol (50 mL) were added along with NaOH (15.00 g, 375.0 mmol) and the reaction was refluxed for 24 hours. The reaction was monitored for the disappearance of the diester using TLC (3:1 hexanes:ethyl acetate mobile phase). The solution was neutralized with conc. HCl and extracted with diethyl ether. Following evaporation of diethyl ether, decalin (30 mL), and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) were added to a 500 mL round bottom flask equipped with a stir bar and a reflux condenser. The flask was lowered into a 190 °C oil bath, and decarboxylation was monitored by the excess frothing caused by the release of CO_2. After the frothing decreased, the reaction was allowed to cool to room temperature. The crude mixture was flashed through a plug of silica gel using hexane as the initial eluent to remove decalin and nonpolar impurities — the decalin could be observed as a clear ring moving through the plug. Once all of the decalin was removed, the eluent was switched to ethyl acetate to remove the desired product (12.3 g, 68 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.31-1.75 (m, 8H), 2.05 (q, 4H), 2.27-2.43 (br, 1H), 4.89-5.06 (m, 4H), 5.69-5.87 (m, 2H) 10.06-11.22 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.75, 31.75, 33.79, 45.52, 114.99, 138.54, 183.24.

Alternative Synthesis of 2-pent-4-enyl-hept-6-enoic acid (3). An alternative synthesis of 2-pent-4-enylhept-6-enoic acid (**3**) was achieved using the methodology described for **2** using 6-heptenoic acid in place of 5-hexenoic acid. The crude acid was purified by distillation (105-115° C, 1 mmHg) yielding 2.30 g (32 %) of the desired compound.

Synthesis of 2-undec-10-enyl-tridec-12-enoic acid (4). Premonomer **3** was synthesized using the methodology applied for premonomer **2**, using undecenyl bromide (28.0 g, 112 mmol), NaH (3.22 g, 60 % in mineral oil, 134 mmol), and diethyl malonate (7.16 g, 44.7 mmol). The saponification was accomplished as discussed above using ethanol (100 mL) and 6 M NaOH (250 mL), and worked up by acidification followed by extraction with diethyl ether. Decarboxylation was accomplished as described above using decalin (25 mL) and catalytic DMAP in a 190 °C oil bath for 1 hour. The crude product was purified using hexane to remove decalin and 3:1 hexanes:ethyl acetate to remove the desired product. The product can be further purified by recrystallization in pentane yielding a white powder (10.5 g, 65 %). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.22-1.55 (br, 28 H), 1.63 (m, 4H), 2.05 (q, 4H), 2.06 (q, br, 4H), 2.37 (m, 1H), 4.98 (m, 4H), 5.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.58, 29.15, 29.34, 29.65, 29.68, 29.75, 29.77, 32.37, 34.03, 45.75, 114.31, 139.44, 183.14.

Synthesis of 1-undec-10-enyl-dodec-11-enylamine (5). Synthesis was performed as described in CH 3.[188]

Synthesis of *N*-(1-undec-10-enyl-dodec-11-enyl)-succinamic acid (6). To a 100 mL round bottom flask equipped with a stir bar under nitrogen was added **4** (2.55 g, 7.61 mmol), succinic anhydride (1.90 g, 19.00 mmol), and a catalytic amount of DMAP in 20 mL of dry THF. The reaction was stirred under argon for 12 hours. Evaporation of THF yielded a white solid, which was purified by recrystallization from CH_3CH_2OH/H_2O to give the pure product in a 67 % yield. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.66 (br, 32 H), 2.04 (q, 4H), 2.51 (t, 2H), 2.70 (t, 2H), 3.78-3.96 (br, 1H), 4.88-5.06(m, 4H), 5.54 (d, br, 1H), 5.72-5.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.07, 29.16, 29.35, 29.69, 29.76, 29.77, 29.79, 30.42, 31.20, 34.03, 35.28, 50.05, 114.33, 139.43, 172.15, 176.72.

Synthesis of (*S*)-2-(2-but-3-enyl-hept-6-enoylamino)-4-methyl-pentanoic acid methyl ester (7). To a stirred solution of 2-but-3-enylhept-6-enoic acid$^{(1.2}$0$^{\text{g, 6.11 mmol}}$), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCL) (1.17 g, 6.11 mmol), and CH_2Cl_2 (50 mL at 0°C) in a 100 ml round bottom flask equipped with a septum and a magnetic stir bar under an Ar purge was added L-leucine methyl ester (0.900 g, 6.2 mmol). The reaction mixture was stirred at 0 °C for 2 hours, followed by the addition of DMAP (0.012 g, 0.6mmol). The solution was allowed to warm gradually to room temperature and stirred overnight. The solution was washed with D.I. H_2O (1 x 25 ml), $NaHCO_3$ (1 x 25 ml), and D.I. H_2O (1 x 25 ml). The organic layer was dried with $MgSO_4$, filtered by Büchner filtration, and concentrated to waxy solid. The crude, waxy product was purified using column chromatography (1:1 hexanes:ethyl acetate), concentrated via rotary evaporation, and dried under vacuum (0.1 mmHg) overnight yielding 1.05 g of white, waxy **7** (36 %). ^{1}H NMR (DMSO-d_6): δ 0.75-0.90(m, 6H), 1.20-1.70(m, 9H), 1.85-2.10(m, 4H), 2.15-2.30(m, 1H), 3.60(s, 3H), 4.25-4.35(m, 1H), 4.85-5.05(m, 4H), 5.65-5.90(m, 2H), 8.20(d, 1H). ^{13}C NMR (DMSO-d_6): δ 21.40, 21.51, 23.63, 24.92, 26.63, 26.75, 31.72, 31.96, 32.54, 32.67, 32.83, 32.91, 33.60, 33.83, 45.38, 45.43, 50.66, 52.30, 115.20, 115.27, 115.33, 115.40, 139.02, 139.20, 139.25, 139.35, 173.73, 173.80, 175.47, 175.48. Anal. Calcd. for $C_{21}H_{29}NO_3$: C 69.86, H 10.10, N 4.53, Found: C 69.95, H 10.36, N 4.39.

General coupling procedure of the amino acid/dipeptides to 3, 4, or 6 using DIC/HOBt. The appropriate amino acid/dipeptide and 1-hydroxybenzotriazole (HOBt)

(2.5 - 5 equiv. to amino acid) were added to a 100 mL round bottom flask. To the flask, equipped with a stir bar and under argon, was added premonomers **3**, **4**, or **6** (1 equiv.), 1,3-diisopropylcarbodiimide (DIC) (1.2 - 2 equiv. to premonomer acid), amino acid/dipeptide (1.2 equiv.), and dry THF (just enough to dissolve the compounds). Finally, NEt_3 (1 equiv. to amino acid) was added to the solution to neutralize the amino acid salt. The reaction vessel was equipped with a reflux condenser heated at 50-60 °C for 12 hours for the amino acids and 48 hours for the peptides. The insoluble urea was removed via gravity filtration, followed by extraction (1 x H_2O, 2 x conc. $NaHCO_3$, 2 x 1$\underline{M}$ HCl). The product was purified with 3 successive recrystallizations using methanol/water (the product was dissolved in hot methanol, and water was added till the solution became cloudy) or by column chromatography.

Synthesis of (*S*)-2-(2-pent-4-enyl-hept-6-enoylamino)-propionic acid benzyl ester (8). The pure product **8** was obtained using the methodology employed above. Purification was obtained by three recrystallizations from CH_3OH/H_2O to yield 44 % of the pure white solid (mp = 71-72 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.28-1.49 (m, 7H), 1.53-1.69 (br, 4H), 1.95-2.10 (br, 5H), 4.68 (p, 1H), 4.88-5.04 (m, 4H), 5.11-5.27 (m, 2H), 5.68-5.85 (m, 2H), 5.98 (d, br, 1H) 7.29-7.46 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.90, 26.93, 27.01, 32.59, 32.63, 33.92, 33.94, 47.80, 48.09, 67.38, 114.894, 128.38, 128.68, 128.86, 135.54, 138.71, 138.77, 173.24, 175.39. Anal. Calcd. for $C_{22}H_{31}NO_3$: C 73.91, H 8.74, N 3.92; Found: C 73.45, H 8.75, N 3.88. EI/HRMS [M + 1]: Calcd for $C_{22}H_{31}NO_3$: 357.2304 g/mol; Found: 357.2311 g/mol.

Synthesis of (*S*)-4-methyl-2-(2-pent-4-enyl-hept-6-enoylamino)-pentanoic acid benzyl ester (9). The pure product **9** was obtained in 74 % yield after purification by column chromatography using 5:1 hexanes:ethyl acetate as the eluent. The product was a wax with a slight yellow tint. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.90 (d, br, 6H), 1.19-1.50 (br, 6H), 1.48-1.70 (br, 5H), 1.91-2.14 (br, 5H), 4.64-4.75 (m, 1H), 4.86-5.02 (m, 4H), 5.07-5.19 (m, 2H), 5.65-5.83 (m, 2H), 5.95 (d, br, 1H), 7.27-7.38 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.00, 23.07, 25.11, 26.91, 26.98, 32.62, 32.73, 33.85, 33.95, 41.73, 47.79, 50.71, 67.20, 114.83, 114.87, 128.43, 128.59, 128.79, 135.63, 138.65, 138.74, 173.17, 178.74. Anal. Calcd. for $C_{25}H_{37}NO_3$: C 75.15, H 9.33, N 3.51; Found: C 74.73, H 9.40, N 3.59. EI/HRMS [M + 1]: Calcd. for $C_{34}H_{64}N_2O_3$: 399.2773 g/mol; Found: 399.2778 g/mol.

Synthesis of (*S*)-4-methyl-2-(2-pent-4-enyl-hept-6-enoylamino)-pentanoic acid methyl ester (10). The pure product **10** was obtained in 80 % yield after purification by column chromatography using 5:1 hexanes:THF as the eluent yielding an opaque wax. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (d, br, 6H), 1.27-1.51 (br, 6H), 1.51-1.72 (br, 5H), 1.96-2.17 (br, 5H), 3.73 (s, 3H), 4.62-4.73 (m, 1H), 4.89-5.07 (m, 4H), 5.70-5.87 (m, 2H), 5.92 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.00, 23.04, 25.10, 26.89, 26.96, 32.62, 32.75, 33.84, 33.94, 41.77, 47.80, 50.56, 52.41, 114.79, 114.82, 138.64, 138.74, 173.79, 175.73. Anal. Calcd. for $C_{19}H_{33}NO_3$: C 70.55, H 10.28, N 4.33; Found: C 70.51, H 10.27, N 4.35. EI/HRMS [M + 1]: Calcd. for $C_{19}H_{33}NO_3$: 323.2460 g/mol; Found: 323.2455 g/mol.

Synthesis of (*S*)-6-benzyloxycarbonylamino-2-(2-pent-4-enyl-hept-6-enoyl-amino)-hexanoic acid methyl ester (11). The pure product **11** was obtained in 55 % yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 77-79 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.19-1.94 (br, 14H), 1.95-2.14 (br, 5H), 3.17 (q, br, 2H), 3.74 (s, 3H), 4.54-4.66 (m, 1H), 4.75-4.88 (br, 1H), 4.89-5.84 (m, 4H), 5.06-5.16 (br, 2H), 5.68-5.86 (m, 2H), 6.05 (d, br, 1H), 7.27-7.42 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.57, 26.92, 27.08, 29.58, 32.20, 32.60, 32.69, 33.87, 33.94, 40.74, 47.80, 51.83, 52.61, 66.87, 114.88, 114.92, 128.34, 128.75, 136.78, 138.71, 138.76, 156.76, 173.20, 175.87. Anal. Calcd. for $C_{27}H_{40}N_2O_5$: C 68.62, H 8.53, N 5.93; Found: C 68.33, H 8.66, N 5.88. EI/HRMS [M + 1]: Calcd. for $C_{27}H_{40}N_2O_5$: 472.2937 g/mol; Found: 472.2937 g/mol.

Synthesis of (*S*)-2-(2-undec-10-enyl-tridec-12-enoylamino)-propionic acid benzyl ester (12). The pure product **12** was obtained in 74 % yield and purified by three recrystallizations from CH_3OH/H_2O (mp = 87-89 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.19-1.46 (br, 32H), 1.48-1.69 (br, 3H), 1.92-2.10 (br, 5H), 4.68 (p, 1H), 4.85-5.04 (m, 4H), 5.10-5.26 (m, 2H), 5.71-5.89 (m, 2H), 5.99 (d, br, 1H) 7.26-7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.13, 27.96, 28.02, 29.38, 29.39, 29.56, 29.57, 29.90, 29.93, 29.97, 30.00, 30.08, 30.12, 33.41, 33.44, 34.25, 48.27, 48.30, 67.52, 114.50, 128.50, 128.83, 129.02, 135.78, 139.63, 139.64, 173.44, 175.88. Anal. Calcd. for $C_{34}H_{55}NO_3$: C 77.66, H 10.54, N 2.66; Found: C 77.46, H 10.53, N 2.66. EI/HRMS [M + 1]: Calcd. for $C_{34}H_{55}NO_3$: 525.4182 g/mol; Found: 525.4190 g/mol.

Synthesis of (*S*) 4-methyl-2-(2-undec-10-enyl-tridec-12-enoylamino)-pentanoic acid tert-butyl ester (13). The pure product **13** was obtained in 78 % yield, and purified by column chromatography using 3:1 hexanes:ethyl acetate as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.13-1.74 (br, 44H), 1.92-2.09 (br, 5H), 4.50-4.61 (m, 1H), 4.88-5.05 (m, 4H), 5.72-5.90 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.31, 23.05, 25.21, 27.78, 27.85 28.21, 29.16, 29.35, 29.71, 29.74, 29.84, 29.92, 33.24, 33.37, 34.03, 42.42, 48.29, 51.18, 81.92, 114.31, 139.47, 172.66, 175.76. Anal. Calcd. for $C_{34}H_{63}NO_3$: C 76.49, H 11.89, N 2.62; Found: C 76.45, H 12.07, N 2.54. EI/HRMS [M + 1]: Calcd. for $C_{34}H_{63}NO_3$: 533.4808 g/mol; Found: 533.4809 g/mol.

Synthesis of (*S*)-4-methyl-2-(2-undec-10-enyl-tridec-12-enoylamino)-pentanoic acid benzyl ester (14). The pure product **14** was obtained in 78 % yield and purified by column chromatography using a 5:1 hexanes:THF mobile phase (mp = 46-48 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.75-1.00 (br, 6H), 1.08-1.47 (br, 30H), 1.47-1.75 (br, 5H), 1.90-2.12 (br, 5H), 4.63-4.79 (br, 1H), 4.85-5.06 (br, 4H), 5.08-5.23 (br, 2H), 5.67-5.94 (m, 2H), 5.95 (d, br, 1H), 7.27-7.46 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.05, 23.08, 25.12, 27.76, 27.85, 29.16, 29.36, 29.71, 29.79, 29.84, 29.92, 33.22, 33.34, 34.04, 41.90, 48.22, 50.65, 67.21, 114.33, 128.41, 128.59, 128.80, 135.63, 139.44, 173.27, 176.02. Anal. Calcd. for $C_{37}H_{61}NO_3$: C 78.25, H 10.83, N 2.47; Found: C 78.12, H 10.91, N 2.49. EI/HRMS [M + 1]: Calcd. for $C_{37}H6_1NO_3$: 567.4651 g/mol; Found: 567.4654 g/mol.

Synthesis of (*S*)-4-methyl-2-(2-undec-10-enyl-tridec-12-enoylamino)-pentanoic acid methyl ester (15). The pure product **15** was obtained in 74 % yield and purified via column chromatography using a 5:1 hexanes:THF mobile phase (mp = 42-44 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.10-1.48 (br, 30H), 1.48-1.73 (br, 5H), 1.93-2.14 (br, 5H), 3.72 (s, 3H), 4.61-4.77 (br, 1H), 4.87-5.11 (m, 4H), 5.71-5.93 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.04, 23.08, 25.12, 27.75, 27.84, 29.15, 29.35, 29.72, 29.76, 29.83, 29.92, 33.25, 33.37, 34.03, 41.92, 48.20, 50.52, 52.40, 114.31, 139.42, 139.44, 173.87, 176.03. Anal. Calcd. for $C_{31}H_{57}NO_3$: C 75.71, H 11.68, N 2.85;

Found: C 75.62, H 11.75, N 2.84. EI/HRMS [M + 1]: Calcd. for $C_{31}H_{57}NO_3$: 491.4338 g/mol; Found: 491.4341 g/mol.

Synthesis of (*S*)-6-benzyloxycarbonylamino-2-(2-undec-10-enyl-tridec-12-enoylamino)-hexanoic acid methyl ester (16). The pure product **16** was obtained in 78 % yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 109-111 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.45 (br, 32H), 1.47-1.94 (br, 6H), 1.96-2.11 (br, 5H), 3.17 (q, br, 2H), 3.73 (s, 3H), 4.56-4.66 (m, 1H), 4.77-4.88 (br, 1H), 4.89-5.84 (m, 4H), 5.06-5.16 (br, 2H), 5.68-5.86 (m, 2H), 6.03 (d, br, 1H), 7.29-7.41 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.56, 27.76, 27.91, 29.16, 29.37, 29.57, 29.70, 29.73, 29.78, 29.86, 29.92, 32.38, 33.17, 33.27, 34.04, 40.75, 48.11, 51.76, 52.57, 66.85, 114.33, 128.32, 128.74, 136.79, 139.46, 156.73, 173.25, 176.19. Anal. Calcd. for $C_{39}H_{64}N_2O_5$: C 73.08, H 10.06, N 4.37; Found: C 73.01, H 10.07, N 4.32. EI/HRMS [M + 1]: Calcd. for $C_{39}H_{64}N_2O_5$: 640.4815 g/mol; Found: 640.4831 g/mol.

Synthesis of arginine-branched monomer (17). The pure product **17** was obtained as a yellow tinted oil in 78 % yield after purification by column chromatography using ethyl acetate as the eluent. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.76 (br, 41H), 1.82-1.97 (m, br, 1H), 1.98-2.17 (br, 8H), 2.54 (s, 3H), 2.60 (s, 3H), 2.97 (s, 2H), 3.13-3.29 (br, 1H), 3.30-3.46 (br, 1H), 3.76 (s, 3H), 4.52-4.64 (br, 1H), 4.89-5.07 (m, 4H), 5.73-5.92 (m, 2H), 6.13-6.23 (br, 2H), 6.30-6.40 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.68, 18.07, 19.46, 25.21, 27.70, 27.83, 28.82, 29.15, 29.36, 29.69, 29.78, 29.84, 29.89, 30.96, 33.06, 33.15, 34.03, 40.84, 43.49, 47.95, 52.82, 86.54, 114.34, 117.64, 124.76, 132.51, 133.35, 138.56, 139.43, 156.33, 158.90, 172.88, 177.31. Anal.

Calcd. for $C_{44}H_{74}N_4O_6S$: C 67.14, H 9.48, N 7.12; Found: C 67.56, H 9.73, N 6.80. EI/HRMS [M + 1]: Calcd. for $C_{44}H_{74}N_4O_6S$: 786.5329 g/mol; Found: 786.5360 g/mol.

Synthesis of (*S*)-6-benzyloxycarbonylamino-2-[3-(1-undec-10-enyl-dodec-11-enylcarbamoyl)-propionylamino]-hexanoic acid methyl ester (18). The pure product **18** was obtained in 72 % yield as a white solid after purification by three recrystallizations using CH_3CH_2OH/H_2O (mp = 131-133 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.10-1.75 (br, 38H), 1.75-1.88 (br, 1H), 1.90-1.96 (br, 1H), 2.02 (q, 4H), 2.36-2.61 (br, 4H), 3.06-3.27 (br, 2H), 3.71 (s, 3H), 3.75-3.90 (br, 1H), 4.46-4.61 (br, 1H), 4.86-5.04 (m, 4H), 5.06-5.22 (br, 3H), 5.58 (d, br, 1H), 5.71-5.91 (m, 2H), 6.68 (d, br, 1H), 7.29-7.39 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.38, 26.06, 26.09, 29.16, 29.36, 29.71, 29.80, 29.87, 31.82, 31.92, 34.03, 35.30, 35.39, 40.62, 49.69, 52.19, 52.55, 66.77, 114.33, 128.28, 128.73, 136.91, 139.45, 156.83, 171.67, 172.46, 172.96. Anal. Calcd. for $C_{42}H_{69}N_3O_6$: C 70.85, H 9.77, N 5.90; Found: C 70.65, H 9.90, N 5.74. EI/HRMS [M + 1]: Calcd. for $C_{42}H_{69}N_3O_6$: 711.5186 g/mol; Found: 711.5252 g/mol.

Synthesis of (*S*)-2-[2-(2-undec-10-enyl-tridec-12-enoylamino)-propionyl-amino]-propionic acid methyl ester (19). The pure product **19** was obtained in 72 % yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 99-100 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.12-1.50 (br, 35H), 1.51-1.67 (br, 3H), 1.94-2.12 (br, 5H), 3.75 (s, 3H), 4.55 (m, 2H), 4.88-5.06 (br, 2H), 5.80 (m, 2H), 5.98 (d, 1H), 6.70 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.26, 18.51, 27.81, 29.15, 29.35, 29.69, 29.76, 29.79, 29.86, 29.93, 33.24, 34.03, 48.00, 48.30, 48.54, 52.67, 114.33, 139.45, 172.15, 173.21,176.28. Anal. Calcd. for $C_{31}H_{56}N_2O_4$: C 71.49, H 10.84, N 5.38; Found:

C 71.47, H 10.80, N 5.33. EI/HRMS [M + 1]: Calcd. for $C_{31}H_{56}N_2O_4$: 520.4240g/mol; Found: 520.4232 g/mol.

Synthesis of (*S*)-4-methyl-2-[4-methyl-2-(2-undec-10-enyl-tridec-12-enoyl-amino)-pentanoylamino]-pentanoic acid methyl ester (20). The pure product **20** was obtained in 71 % yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 57-59 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.85-1.01 (m, 12H), 1.12-1.47 (br, 30H), 1.48-1.72 (br, 8H), 1.94-2.08 (br, 5H), 3.73 (s, 3H), 4.43-4.64 (br, 2H), 4.88-5.06 (m, 4H), 5.72-5.92 (br, 3H), 6.51 (d, br, 1H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.03, 22.24, 23.03, 23.16, 24.91, 24.96, 27.85, 29.16, 29.35, 29.70, 29.73, 29.83, 29.97, 33.16, 33.34, 34.06, 40.92, 41.67, 48.22, 50.93, 51.40, 52.51 114.35, 139.46, 171.99, 173.24, 176.49. Anal. Calcd. for $C_{37}H_{68}N_2O_4$: C 73.46, H 11.33, N 4.63; Found: C 73.27, H 11.41, N 4.49. EI/HRMS [M + 1]: Calcd. for $C_{37}H_{68}N_2O_4$: 604.5179 g/mol; Found: 604.5178 g/mol.

Synthesis of (*S*)-(*S*)-(*S*)-2-{2-[2-(2-Undec-10-enyl-tridec-12-enoylamino)-propionylamino]-propionylamino}-propionic acid methyl ester (21). The synthesis of **21** was performed using the general methodology above, except that DMF had to be used as the solvent due to insolubility of the starting tripeptides and the product **39**. Workup was also different since DMF was used. First the urea salts were filtered, and washed with D.I. water. The addition of excess D.I. water resulted in a precipitate that was filtered and this process was repeated till no more precipitate formed. This yielded a pink powder that was purified by column chromatography using hexanes:ethyl acetate (1:1) as the mobile phase. There were still two spots by TLC, so another column was run using 3:1 hexanes:acetone as the eluent. The product was still not 100 % pure, so a recrystallization was performed in acetone yielding 320 mg of the desired compound in 23 % yield (mp = 166-168 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.12-1.59 (br, 41H), 2.05 (q, br, 5H), 3.79 (s, 3H), 4.40-4.60 (m, 3H), 4.91-5.12 (br, 4H), 5.78-5.91 (m, 2H), 5.98 (d, 1H), 6.61 (d, 1H), 6.71 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.45, 18.75, 19.06, 27.82, 29.15, 29.35, 29.69, 29.90, 33.18, 34.02, 47.73, 48.25, 48.63, 49.02, 52.67, 114.34, 139.42, 171.91, 172.63, 173.43, 176.37. Anal. Calcd. for $C_{34}H_{61}N_3O_5$: C 69.00, H 10.39, N 7.10; Found: C 68.27, H 10.32, N 6.77.

Polymer Synthesis

General synthesis. Polymerization of the monomers containing amino acid and peptide entities differs somewhat from a typical ADMET polymerization. These monomers are solids at or near room temperature, and so a small amount of solvent is necessary to conduct the chemistry in the liquid state under mild polymerization conditions. The procedure is described as follows. Monomer is placed in a 50 or 100 mL schlenk tube equipped with a stir bar and a septum, followed by the addition of the second generation Grubbs' Ru catalyst (**1**) (100:1/monomer:catalyst); both additions are done while maintaining a positive Ar flow throughout the system, followed by flushing with Ar for 30 minutes after the additions are complete. A minimal amount of dry THF then is added via syringe to produce a homogeneous solution, and the reaction mixture is allowed to stir for 144 hrs at 50 °C. This lengthy reaction time is done to assure complete conversion, which is necessary during a step polymerization; shorter reaction times likely are feasible. Dry THF was added periodically to replace solvent lost to evaporation. The reaction is sampled and assessed for complete conversion via ^{1}H NMR, and if necessary, additional catalyst is added and the solution is allowed to stir for a longer period of time.

Once conversion is complete, the ruthenium catalyst is removed via complexation by treatment with tris(hydroxymethyl) phosphine (THP). Doing so is accomplished by dissolving the reaction mixture in chloroform (~30 mL), combining this solution with a tris(hydroxymethyl) phosphine solution (1M in isopropanol, 30 equiv. to catalyst), then extracting this solution with 1M HCl (1 x 20 mL), conc. $NaHCO_3$ (1 x 20 mL), and conc. NaCl (1 x 20 mL). The polymer solution that remains is dried over $MgSO_4$, followed by rotary evaporation to yield the pure polymer. These polymers can be solvent-cast from chloroform on a Teflon™ plate to yield a thin film.

Characterization of 22. ^1H NMR (300 MHz, DMSO-d_6, 70 °C, ppm) δ: 0.75-0.90(m, 6H), 1.20-1.70(m, 9H) 1.85-2.10(m, 4H), 2.15-2.30(m, 1H), 3.60(s, 3H), 4.25-4.35(m, 1H), 5.30-5.50(m, 2H), 8.20(m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, 70 °C, ppm): δ 21.62-21.71(br), 23.70, 23.66, 25.12, 25.24, 23.45-23.72(m), 30.69-30.77(m), 32.25-33.02(m), 45.61-46.27(m), 50.62-50.96(m), 50.92, 52.41-52.69(br), 52.70, 130.31-130.93(m), 173.82-174.08(m), 175.72-175.96.

Characterization of 23. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.07-1.73 (br, 7H), 1.74-2.19 (br, 5H), 4.53-4.74 (p, 1H), 5.04-5.39 (br, 4H), 5.94-6.56 (br, 1H), 7.27-7.41 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.82, 26.80, 27.75, 32.55, 32.84, 48.07, 48.42, 67.30, 67.40, 128.33, 128.40, 128.65, 128.85, 130.42, 131.47, 135.59, 173.21, 175.62.

Characterization of 24. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.77-.97 (br, 6H), 1.10-1.45 (br, 6H), 1.45-1.74 (br, 5H), 1.78-2.18 (br, 5H), 4.59-4.77 (br, 1H), 5.03-5.20 (br, 2H), 5.20-5.39 (br, 2H), 5.80-6.05 (br, 1H), 7.27-7.41 (br, 5H). ^{13}C NMR (75 MHz,

$CDCl_3$, ppm): δ 22.06, 23.09, 25.10, 27.74, 32.74, 41.73, 47.89, 50.71, 67.19, 128.41, 128.60, 128.81, 130.34, 135.63, 173.28, 175.90.

Characterization of 25. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.18-1.49 (br, 6H), 1.50-1.78 (br, 5H), 1.82-2.27 (br, 5H), 3.72 (s, 3H), 4.58-4.73 (br, 1H), 5.26-5.50 (br, 2H), 5.94-6.18 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$-d_6, ppm): δ 22.01, 23.08, 25.09, 27.58, 27.67, 30.52, 32.70, 41.69, 47.80, 50.56, 52.39, 130.40, 130.70, 173.78, 175.85.

Characterization of 26. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.08-1.74 (br, 13H), 1.74-2.20 (br, 6H), 3.00-3.22 (br, 2H), 3.67 (s, br, 3H), 4.46-4.66 (m, 1H), 4.95-5.16 (br, 2H), 5.16-5.43 (m, 3H), 6.11-6.67 (br, 1H), 7.23-7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.68, 27.64, 29.54, 29.92, 30.54, 31.94, 32.79, 40.74, 47.58, 51.89, 52.54, 66.74, 128.21, 128.27, 128.56, 128.71, 130.36, 136.85, 156.86, 173.23, 176.13

Characterization of 27. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.07-1.49 (br, 32H), 1.50-1.69 (br, 3H), 1.84-2.13 (br, 5H), 4.58-4.76 (p, 1H), 5.09-5.26 (br, 2H), 5.28-5.49 (br, 2H), 6.01-6.21 (br, 1H), 7.24-7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.85, 27.78, 27.84, 29.44, 29.78, 29.91, 32.86, 33.26, 48.05, 67.29, 128.32, 128.63, 128.84, 130.58, 135.61, 173.25, 175.77.

Characterization of 28. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (d, br, 6H), 1.13-1.77 (br, 44H), 1.87-2.11 (br, 5H), 4.50-4.63 (m, 1H), 5.28-5.47 (br, 2H), 5.83 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.28, 23.05, 25.18, 27.43, 27.79, 27.86, 28.19, 29.42, 29.54, 29.76, 29.80, 29.89, 32.83, 33.26, 33.39, 42.36, 48.26, 51.16, 81.86, 130.54, 172.63, 175.75.

Characterization of 29. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0..92 (d, br, 6H), 1.09-1.47 (br, 30H), 1.48-1.70 (br, 5H), 1.85-2.11 (br, 5H), 4.72 (m, br, 1H), 5.10-5.21 (br, 2H), 5.29-5.41 (br, 2H), 5.86 (d, br, 1H), 7.29-7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.04, 23.10, 25.12, 27.80, 27.89, 29.44, 29.77, 29.88, 32.85, 33.27, 33.39, 41.85, 48.22, 50.65, 67.18, 128.40, 128.57, 128.79, 130.56, 135.65, 173.24, 176.02

Characterization of 30. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.14-1.47 (br, 30H), 1.49-1.72 (br, 5H), 1.89-2.12 (br, 5H), 3.73 (s, 3H), 4.68 (br, m, 1H), 5.28-5.46 (br, 2H), 5.78-5.96 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.03, 23.08, 25.11, 27.43, 27.77, 27.87, 29.42, 29.55, 29.77, 29.82, 29.89, 32.83, 33.28, 33.41, 41.88, 48.20, 50.52, 52.39, 130.56, 173.86, 176.03

Characterization of 31. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.09-1.76 (br, 38H), 1.90-2.16 (br, 5H), 3.02-3.23 (br, 2H), 3.71 (s, 3H), 4.52-4.66 (br, 1H), 4.99-5.25 (br, 3H), 5.28-5.45 (br, 2H), 6.26-6.44 (br, 1H), 7.24-7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.59, 25.81, 27.74, 27.89, 29.40, 29.53, 29.76, 29.86, 31.98, 32.82, 33.17, 33.29, 40.65, 47.89, 51.81, 52.43, 66.69, 128.18, 128.22, 128.66, 130.52, 136.85, 156.82, 173.21, 176.29.

Characterization of 32. ^{1}H NMR (300 MHz, DMSO-d_6, 70 °C, ppm): δ 0.96-1.81 (br, 42H), 1.84-2.29 (br, 8H), 2.39-2.66 (br, 6H overlapping with DMSO-d_6 resonance), 2.89-3.19 (br, 4H), 3.61 (s, br, 3H), 4.14-4.33 (br, 1H), 4.23-4.46 (br, 2H), 6.48-7.33 (br, 3H), 8.12-8.32 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, 70 °C, ppm): δ 12.70, 18.03, 19.36, 26.26, 27.30, 27.49, 28.89, 29.14, 29.61, 31.18, 32.54, 32.98, 33.16, (note some peaks under DMSO-d_6 resonance) 43.36, 46.06, 52.01, 52.25, 86.75, 116.84, 124.87, 130.65, 132.15, 137.84, 156.93, 158.20, 173.06, 175.87.

Characterization of 33. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.09-1.77 (br, 36H), 1.77-2.06 (br, 6H), 2.40-2.63 (br, 4H), 3.06-326 (br, 2H), 3.72 (br, s, 3H), 3.79-3.90 (br, 1H), 4.47-4.61 (br, 1H), 5.04-5.17 (br, 2H), 5.22-5.47 (br, 3H), 5.69-6.13 (br, 1H), 6.69-7.02 (br, 1H) 7.20-7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.69, 26.37, 29.62, 29.97, 30.09, 32.05, 33.04, 35.64, 40.86, 49.90, 52.44, 52.69, 66.94, 128.43, 128.88, 130.76, 137.14, 157.00, 171.86, 172.66, 173.10.

Characterization of 34. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.10-1.46 (br, 35H), 1.47-1.68 (br, 3H), 1.89-2.13 (br, 5H), 3.74 (s, 3H), 4.52 (br, m, 1H), 4.59-4.76 (br, 1H), 5.07 (m, 4H), 5.72-5.91 (m, 2H), 5.98 (d, br, 1H), 6.70 (d, br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 17.97, 18.79, 25.82, 27.39, 27.80, 29.35, 29.75, 29.86, 32.80, 33.24, 47.83, 48.29, 48.49, 52.57, 130.56, 172.54, 173.22,176.26.

Characterization of 35. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.92 (m, 12H), 1.10-1.47 (br, 30H), 1.47-1.73 (br, 8H), 1.86-2.13 (br, 5H), 3.73 (s, 3H), 4.47-4.66 (br, 2H), 5.28-5.47 (br, 2H), 6.02-6.39 (br, 1H), 6.79-7.09 (br, 1H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.06, 22.38, 22.99, 23.12, 24.88, 24.96, 27.83, 29.39, 29.74, 29.86, 32.80, 33.16, 33.34, 41.10, 41.41, 48.04, 50.94, 51.44, 52.37 130.08, 130.54, 172.25, 173.18, 176.39.

Characterization of 36. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 0.93-1.62 (br, 41H), 1.81-2.25 (br, 5H), 3.58 (s, 3H), 4.11-4.38 (br, 3H), 5.22-5.45 (br, 2H), 7.66-7.82 (br, 1H), 7.88-8.03 (br, 1H), 8.18-8.36 (br, 1H). ^{13}C NMR was not obtained due to a lack of solubility of the polymer even in hot DMSO-d_6.

Results and Discussion

Monomer Synthesis

To synthesize "*N*-terminus" bio-olefins, an acid branched α,ω diene is required. This can be accomplished by forming the enolate dianion of the appropriate alkenyl acid using two equivalents of LDA, followed by the S_N2 reaction with 5-bromo pentene to give the desired premonomers **2** and **3** (Figure 4-1). This reaction suffered from low yields, probably due to the insolubility of the enolate. In addition to the low yields, a lack of availability of the starting alkenyl acids and the high toxicity of hexamethylphosphoramide (HMPA) made this synthesis undesirable.

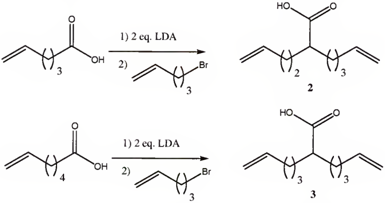
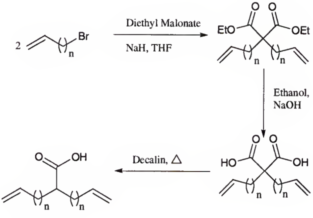


Figure 4-1. Synthesis of premonomer **2** and the alternative synthesis of premonomer **3**.

The unfavorable attributes of the synthesis shown in Figure 4-1, led to the development of a new synthetic methodology. Mr. Travis Baughman in the Wagener Research Group spearheaded the pursuit of this methodology. Figure 4-2 demonstrates the chosen synthesis of premonomers **3** and **4**, which was accomplished via two consecutive S_N2 reactions between the deprotonated diethyl malonate and the corresponding alkenyl halide to form the diester (Figure 4-2). The reaction mixture was allowed to stir overnight under reflux, and was easily monitored for complete conversion by TLC. In most cases excess NaH and alkenyl bromide were added to force the reaction to completion and in the case of premonomer **4**, undecenyl iodide was used as well. Doing so gave similar overall yields as the bromide; however, the initial diester synthesis was completed after only 4 hours as determined by TLC. Neutralization of the NaH with water, addition of ethanol and NaOH, and refluxing overnight resulted in successful saponification to the desired diacid. The crude product was dissolved in a minimal amount of decalin — just enough to dissolve the diacid when hot — a procedure that led to rapid decarboxylation at 190 °C as evidenced by the vigorous bubbling. The large difference in polarity of the product, starting material, and decalin permitted easy purification by flash chromatography. Decalin can be removed using hexane as the eluent, a procedure simplified by the fact that decalin is observed as a clear band in the silica gel. Switching to a more polar eluent, *i.e.* adding ethyl acetate, removed the desired product. In addition, further purification of premonomer **4** is possible via recrystallization in pentane.



3) n = 3
4) n = 9

Figure 4-2. General synthetic scheme for the preparation of premonomers **3** and **4**.

The succinic acid branched premonomer **6** (Figure 4-3) was prepared by reacting amine **5**, which was synthesized as reported previously,[188,189] with succinic anhydride and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction occurred rapidly, and the product was purified by recrystallization from CH_3CH_2OH/H_2O giving the desired acid in 67 % yield. Succinic anhydride was used without purification, which could have led to a lower reaction yield due to the presence of unreactive succinic acid.

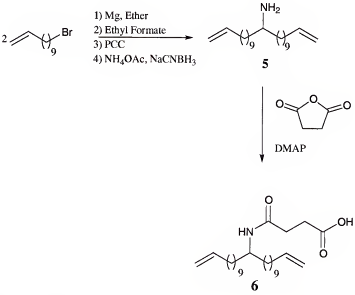


Figure 4-3. Synthesis of the succinic acid branched premonomer **6**.

The first "*N*-terminus" monomer prepared was the leucine methyl ester branched monomer **7**. This monomer was prepared using the method described by Sanda and Endo for coupling amino alcohols to alkenyl acids using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) as the coupling reagent and 4-dimethylaminopyridine (DMAP) as the catalyst.[147] This reaction suffered from low yields (36 %). A review of the literature demonstrated that 1,3-dicyclohexylcarbodiimide (DCC) or 1,3-diisopropylcarbodiimide (DIC) with 1-hydroxy-benzotriazole (HOBt) was the method commonly employed for coupling peptides,[190, 191] primarily due to the higher reactivity of these carbodiimides over EDC·HCl. In addition, DMAP has been linked to racemization during these reactions, a phenomenon not observed when HOBt is used.

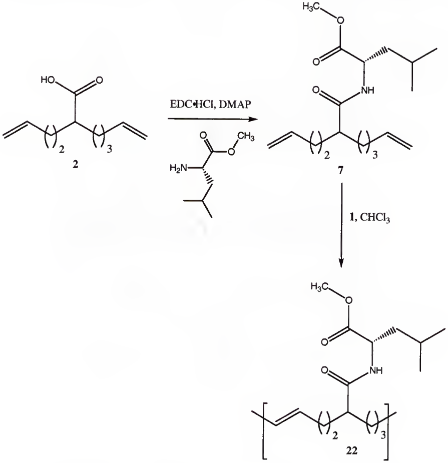
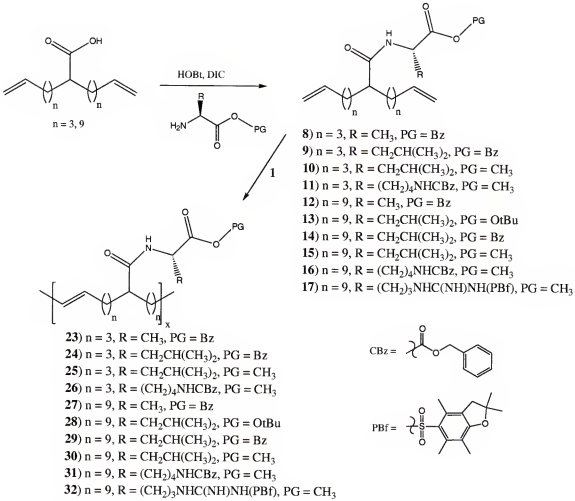


Figure 4-4. Synthesis of monomer **7** and polymer **22** using the procedure by Sanda and Endo.[147]

Due to the low yields achieved for monomer **7**, some adjustments were made on the synthesis of the rest of the monomers. Specifically, the amino acids/dipeptides were coupled to premonomers **3**, **4**, and **6** using DIC (1.5 – 2 equivalent), which was chosen due to its liquid nature facilitating the ease of use, as the coupling reagent with HOBt (2.5 – 5 equivalents) as the catalyst/additive in THF (Figure 4-5). Triethylamine (1 equivalent) was added to neutralize the amino acid salt, and the reactions were stirred at 50 – 60 °C for 12 to 48 hours; the dipeptides were given more time to react, as previously determined to be necessary.[188] Once finished, the triethylamine hydrochloride and urea salts were removed by gravity filtration, and the THF was removed by rotary evaporation. The crude product was dissolved in methylene chloride, and washings were performed to remove excess triethylamine, premonomer, amino acid/dipeptide, and HOBt. The order of the washings proved important — a solid precipitated in the separatory funnel if HCl was added first, while no problems were encountered when concentrated $NaHCO_3$ was used for the initial washing. The monomers were purified either by recrystallization or column chromatography, characterized by elemental analysis, HRMS, ^1H NMR, and ^{13}C NMR and assessed for purity by TLC prior to polymerization.

The amino acid branched dienes **8**, **9**, **10**, and **11,** which possess 3 methylene units between the olefin and branch point, were prepared by coupling premonomer **3** with H-Ala-OBz·HCl, H-Leu-OBz·p-tosylate, H-Leu-OMe·HCl, and H-Lys(CBz)-OMe·HCl, respectively (Figure 4-5). Monomers **8** and **11** were purified via three recrystallizations using CH_3OH/H_2O to give the pure compounds in 44 % and 55 % yield. These yields were low due to the rather high solubility of the compounds in methanol. Monomers **9** and **10** are waxy solids, and were thus purified by column chromatography using 5:1 hexanes:ethyl acetate and 5:1 hexanes:THF as the eluent, respectively. The compounds were recovered in 74 % yield for **9** and 80 % yield for **10**, which also suggests that the recrystallization method used for monomers **8** and **11** was the cause of the lower yields.



8) n = 3, R = CH_3, PG = Bz
9) n = 3, R = $CH_2CH(CH_3)_2$, PG = Bz
10) n = 3, R = $CH_2CH(CH_3)_2$, PG = CH_3
11) n = 3, R = $(CH_2)_4NHCBz$, PG = CH_3
12) n = 9, R = CH_3, PG = Bz
13) n = 9, R = $CH_2CH(CH_3)_2$, PG = OtBu
14) n = 9, R = $CH_2CH(CH_3)_2$, PG = Bz
15) n = 9, R = $CH_2CH(CH_3)_2$, PG = CH_3
16) n = 9, R = $(CH_2)_4NHCBz$, PG = CH_3
17) n = 9, R = $(CH_2)_3NHC(NH)NH(PBf)$, PG = CH_3

23) n = 3, R = CH_3, PG = Bz
24) n = 3, R = $CH_2CH(CH_3)_2$, PG = Bz
25) n = 3, R = $CH_2CH(CH_3)_2$, PG = CH_3
26) n = 3, R = $(CH_2)_4NHCBz$, PG = CH_3
27) n = 9, R = CH_3, PG = Bz
28) n = 9, R = $CH_2CH(CH_3)_2$, PG = OtBu
29) n = 9, R = $CH_2CH(CH_3)_2$, PG = Bz
30) n = 9, R = $CH_2CH(CH_3)_2$, PG = CH_3
31) n = 9, R = $(CH_2)_4NHCBz$, PG = CH_3
32) n = 9, R = $(CH_2)_3NHC(NH)NH(PBf)$, PG = CH_3

Figure 4-5. Synthesis of the protected amino acid branched monomers and polymers.

Monomers **12**, **13**, **14**, **15**, **16**, and **17** with 9 methylene units between the branch point and the olefin were synthesized by coupling premonomer **4** to H-Ala-OBz·HCl, H-Leu-OtBu·HCl, H-Leu-OBz·HCl, H-Leu-OMe·HCl, H-Lys(CBz)-OMe·HCl, H-Lys(Boc)-OtBu·HCl and H-Arg(PBf)-OMe·HCl (Figure 4-5). Monomers **12** and **13** were purified by recrystallization using the CH_3OH/H_2O method in high yields, 74 % and 78 %, respectively. Monomer **13** was purified by flash chromatography using 3:1 hexanes:ethyl acetate as the eluent giving the pure product as a yellow-tinted oil in 78 % yield. In the case of monomers **14** and **15**, 5:1 hexanes:THF was employed as the mobile phase, which gave the pure products as opaque waxes in 78 % and 74 % yield, respectively. Monomer **17** was recovered in pure form as an oil in 78 % yield — the liquid nature of the monomer is probably due to the PBf protecting group — after purification by flash column chromatography using ethyl acetate as the eluent.

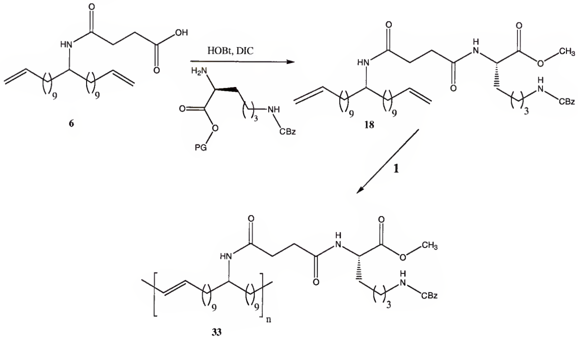


Figure 4-6. Synthesis of the lysine branched monomer separated from the diene with a succinic acid spacer.

Monomer **18** was synthesized having a succinic acid linkage between the polymer backbone and the amino acid in order to investigate the effect of a “spacer” between the amino acid functionality and the polymer backbone (Figure 4-6). Premonomer **6** was coupled to H-Lys(CBz)-OMe·HCl using the same methodology discussed above, and purified by recrystallization from CH_3OH/H_2O to give the desired product as a white powder in 72 % yield.

The dipeptide branched monomers, **19** and **20,** were prepared by coupling premonomer **4** to H-Ala-Ala-OMe·HCl and H-Leu-Leu-OMe·HBr, respectively (Figure

4-7). The reactions were allowed to stir 48 hours, an amount of time previously determined to give high yields for dipeptide branched monomers.[188-189] These monomers were obtained as white solids after purification using the recrystallization method described above, and recovered in good yields, 72 % and 71 %, respectively.

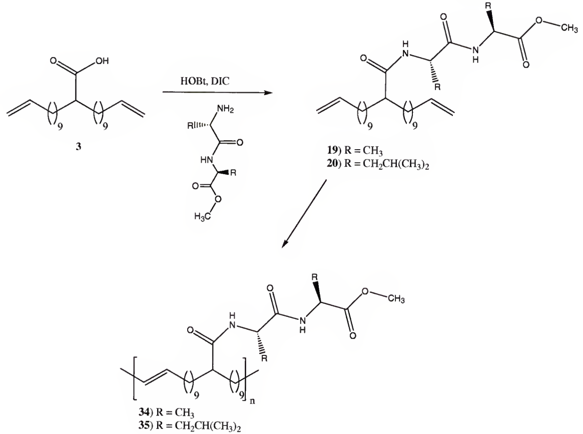


Figure 4-7. Synthesis of the dipeptide branched monomers and polymers.

Polymer	$\overline{M}_w$ ^{a}(g/mol)	PDI^a	T_m^{b}(°C)	T_g^{b}(°C)
22	63,000^c	2.02	114^d	f
23	26,000	1.54	g	28
24	36,000	1.45	g	18
25	73,000	1.55	132	f
26	63,000	1.67	g	7
27	21,000	1.62	38^e	-21
28	25,000	1.91	g	5
29	42,000	1.85	g	-10
30	29,000	1.59	g	3
31	44,000	1.80	79	f
32	26,000	1.40	g	69
33	73,000	1.50	106	5
34	21,000	1.40	71^e	f
35	38,000	1.64	74	f

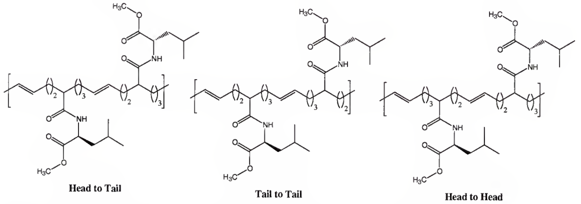
Table 4-1. The GPC and DSC data for the "*N*-terminus" bio-olefins. a) Weight average molecular weight and PDI values were calculated by GPC using LALLS. b) Data obtained using a Perkin Elmer DSC 7 at 10 °C/ minute. c) Calculated from the number average molecular weight, which was determined by GPC relative to polystyrene. d) Data obtained from Dr. Krystyna Brzezinska at the University of California in Santa Barbara. e) The T_m reported is that of the solvent crystallized sample; no T_m was observed from the melt crystallized sample. f) No T_g observed over the scanned range of -80 °C to 180 °C. g) No T_m observed over the scanned range of -80 °C to 180 °C.

Polymer Synthesis

Acyclic diene metathesis (ADMET) is a simple step polymerization that allows for precise branch and/or functionality placement along the polymer backbone, where this structural feature is "built in" prior to polymerization by way of appropriate monomer design. Thus, ADMET permits the synthesis of polymers incapable of being prepared via common polymerization methods.[192] Since all of the monomers described herein are solids or become a solid after minimal couplings, the polymerizations were run in a minimal amount of solvent (THF) under an Ar purge to aid in the removal of ethylene (an illustration of this apparatus can be seen in Ch. 3, Figure 3-5).

This methodology produces polymers of approximately the same molecular weight as those obtained under typical ADMET condition using high vacuum (Table 1).[188,189,192] Initially, dry $CHCl_3$ was used to polymerize monomers **7** and **10**. However, due to the findings discussed in the previous chapter, dry THF was chosen as the solvent for the second polymerization of **10** and the rest of the monomers discussed herein; most *C*-terminus monomers were incapable of polymerization in $CHCl_3$.[188] Apparently the solvent participates in the polymerization mechanism itself by shifting the dynamic equilibrium complex of monomer functionality and catalyst towards the free catalyst state; thus, the catalyst is available for polymerization chemistry.

In chapter 3 the synthesis of polyolefins containing amino acids and dipeptides attached through the *C*-terminus were discussed and found to have good thermal and mechanical properties, *e.g.* T_ms up to 150 °C and moduli up to 220 MPA.[188,189] Indeed the first branched bio-olefins prepared came from the polymerization of the leucine methyl ester branched monomers **7** and **10** with the amino acid attached through the *N*-terminus.[148,150,187] Monomer **7** is very interesting given its unsymmetrical nature causing a variety of possible monomer repeat unit configurations as shown in Figure 4-8, which can be seen in the ^{13}C NMR of the polymer. Both polymer **22** and **25** were polymerized to high molecular weight polymers (Table 4-1). The fact that both polymerize demonstrates a difference in reactivity between "*C*-terminus" and "*N*-terminus" monomers towards metathesis, since the monomers with three methylene units failed to polymerize with catalyst **1** when the amino acid was attached through the *C*-terminus. In addition to this higher observed reactivity, polymers **22** and **25** appeared to have good mechanical properties with high melting temperatures, intriguing properties spawning the work described in Chapter 3 and this chapter.



Head to Tail

Tail to Tail

Head to Head

Figure 4-8. Possible configurations of the repeat units for polymer **22**.

Consequently, we felt it advantageous to investigate further the synthesis and properties of polymers with amino acids/dipeptides attached through the *N*-terminus on every 9th and 21st carbon of the backbone, and to compare these results with those polymers prepared previously having amino acid/peptide moieties attached through the *C*-terminus. The alanine branched monomer **8** was polymerized to polymer **23** having a molecular weight ($\overline{M_w}$ obtained by light scattering) of 26,000 g/mol (Table 4-1 and Figure 4-5). After only a few hours, the growing polymer became insoluble resulting in a gel-like mixture; however, it appears the polymerization continues to occur even in this gel-like state, suggesting that a high degree of polymer/monomer solubility may not be required for high polymer preparation. This observation could become important when applying this methodology to larger peptides, which tend to lack solubility in common organic solvents. The resulting polymer **23** was only slightly soluble in common organic solvents, which led to easy purification of the polymer by precipitation in hexanes.

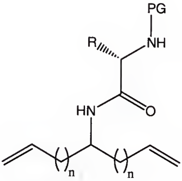
The leucine benzyl ester monomer **9** was converted to polymer **24**, but with some difficulty. End groups were detectable in the ^{1}H NMR after the first polymerization attempt, a sign of incomplete conversion, so the polymer was dissolved in THF and exposed to additional catalyst (100:1 initial monomer: catalyst), which yielded high polymer with a $\overline{M_w}$ of 36,000 g/mol (Table 4-1). Monomer **10**, which was prepared for the second time for this study, and monomer **11** were easily converted to high polymers **25** and **26** having $\overline{M_w}$s of 73,000 and 63,000 g/mol, respectively (Figure 4-5). Interestingly, polymer **25** was prepared this time using THF as the solvent yielding a similar weight average molecular weight as reported for the initial results using $CHCl_3$ (73,000 g/mol in THF versus 55,000 g/mol in $CHCl_3$). In addition, several "*N*-terminus" polymers with alanine, leucine, and lysine branches (**27** – **31** in Figure 4-5) were prepared possessing an amino acid branch on every 21st carbon, and all of these polymers are high in molecular weight (Table 4-1).

The orientation of the amino acid entity with respect to the polymer backbone influences the reactivity of the diene towards ADMET chemistry, regardless of the frequency of appearance of the amino acid along the hydrocarbon polymer backbone. For example, "*N*-terminus" polymers **23** and **24** (those which have the amino acid attached via the *N*-terminus), and which have the amino acid attached on each and every 9th carbon, can be synthesized in high molecular weight, whereas the previously reported "*C*-terminus" monomers **37** and **38** (Figure 4-9) only yield oligomers. This phenomenon is even observed when the amino acid appears on each and every 21st carbon; the highly polar arginine-based "*C* terminus" monomer **39** (Figure 4-9) does not polymerize to high molecular weight, whereas the similar "*N*-terminus" monomer **17** (Figure 4-5) does. This observation likely is a result of the intramolecular complexation, mentioned above, being more of a factor in the mechanism of the "*C*-terminus" monomer polymerization than for the "*N*-terminus" polymerization. Further, the arginine moiety is the most polar entity of the biologically active peptide sequence arginine-glycine-aspartic acid (RGD),[165,166,193] which is a target molecule for the preparation of a biologically active bio-olefin; thus, the polymerizability of monomer **17** is an important result towards the preparation of biologically active polymers.

In addition to the high molecular weight obtained for polymer **32**, an interesting an unexpected result was observed. Although the monomer was soluble in a variety of solvents, *e.g.* $CHCl_3$, CH_2Cl_2, and THF, the polymer was only slightly soluble in hot THF and DMSO. During the removal of the catalyst using the methodology described previously in $CHCl_3$, a white coating of polymer formed on the glassware, which upon addition of ethyl acetate formed a tacky aggregate that was easily isolated. Further, addition of concentrated $NaHCO_3$ solution broke up the aggregation producing a granular material that was easily filtered and purified by washing with DI H_2O to yield polymer **32** as a white, fibrous material.

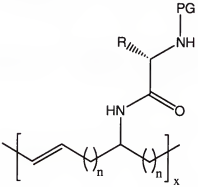
We also investigated the effect of inserting a "spacer" molecule between the hydrocarbon backbone and the amino acid. Lysine was chosen as the amino acid for this study, since it has shown to produce crystalline polymers when located on each and every 21st carbon of the polymer chain. The monomer synthesis and polymerization are trivial (Figure 4-6), yielding a high molecular weight bio-olefin, **33**. Further, a comparison of

33 with the lysine branched polymers **31** (Figure 4-5) and **40** (Figure 4-10) should give an interesting insight on the effect of a spacer on the semicrystallinity of the resulting polymer.



37) n = 3, R = CH_3, PG = BOC
38) n = 3, R = $CH_2CH(CH_3)_2$, PG = BOC
39) n = 9, R = $(CH_2)_3NHCN(CBz)NHCBz$, PG = CBz

Figure 4-9. The "C-Terminus" amino acid branched monomers incapable of being polymerized using catalyst **1**.



40) n = 9, R = $(CH_2)_4NHCBz$, PG = CBz

Figure 4-10. Previously reported lysine branched polymer attached through the C-terminus.[188-189]

Dipeptide branched monomers also are amenable to this polymerization methodology, which converts monomers **19** and **20** (Figure 4-7) into polymers **34** and **35**, both high in molecular weight as well (Table 4-1). Peptides, of course, are of interest since the goal of this research is to generate high strength materials possessing surfaces designed for biological activity. The fact that highly polar monomers such as **19** and **20** are capable of ADMET polymerization speaks well of the utility of the ruthenium-based metathesis catalysts.

Thermal Characterization

Generating durable materials capable of being shaped into useful biologically active structures usually means working with polymers that either have a high glass temperature or a reasonably high degree of crystallization. A considerable number of these bio-polymers are film-forming (Figure 4-11) and indeed crystallize, which likely is a result of both the regularity of spacing of the amino acid group along the hydrocarbon backbone, coupled with the strong interactions between amino acid and peptide groups. The crystallinity within these materials is manifested in terms of tensile strength and toughness, which for some of the polymers roughly matches that of low density polyethylene.[182,188,189]

Differential scanning calorimetry was used to determine which samples were semicrystalline. We found that roughly half of the *N*-terminus bio-olefins prepared to date crystallize; those which appear to be completely amorphous exhibit glass transitions in the range of –10 °C to 69 °C, while those which are semicrystalline exhibit melting points between 40 °C and 132 °C (Table 4-1). Both of the dipeptide branched bio-olefins are semicrystalline. Further, the initial wide-angle x-ray work on many of these polymers suggests they possess a high degree of crystallinity. It appears that the size and polarity of the amino acid and dipeptide entities influence the nature of the crystallization that we observe.

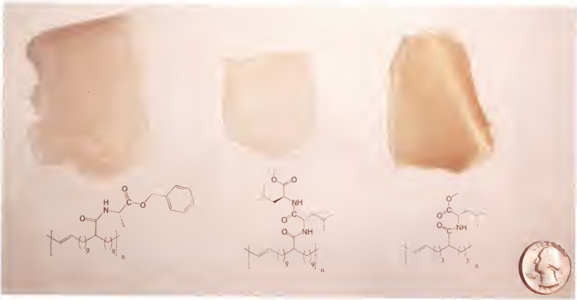


Figure 4-11. Film-forming bio-olefins **27** (left), **30** (middle), and **25** (right), demonstrating the material nature of these polymers.

Only two of the leucine-containing polymers are semicrystalline. Polymers **21**, which due to the unsymmetrical nature can have a leucine methyl ester branch on every 7th, 8th, or 9th carbon (Figure 4-8), and polymer **25**, which a branch on each and every 9th carbon, exhibit the highest melting points obtained for amino acid branched bio-olefins as well (115 and 132 °C, respectively). As shown in Figure 4-8, the unsymmetrical nature of monomer **7** leads to several different arrangements of the polymer repeat units. The fact that this polymer is semicrystalline is confusing, since this added randomness should inhibit or suppress crystallization. Further, it is interesting to compare these polymers with **30**, which differs only in the location of the branch – polymer **25** possesses a leucine methyl ester branch on every 9th carbon versus every 21st carbon for polymer **30**. One might predict that polymer **30** should be semicrystalline as well, but that is not the case. Also interesting is the comparison of the lysine branched polymers **26** and **31**, which again are identical in structure with the exception of the distance between points of attachment of the amino acid branches. This time the order is reversed: the longer spaced bio-olefin (amino acid on every 21st carbon) crystallizes while the other does not. These findings are in agreement with those reported in CH. 3 for the "*C*-terminus" polymers.

The lysine branched polymer **33** possessing a succinic acid "spacer" separating the amino acid from the backbone is semicrystalline similar to the findings of the lysine branched polymer without the spacer linkage. However, its DSC curve exhibits what may be a cold crystallization phenomenon (Figure 4-12). The first scan reveals an isomorphic response, with a "premelt" appearing at about 60 °C, followed by a higher melting response at about 105 °C. The cold crystallization phenomenon, if indeed that is what we observe, is apparent at around 60 °C followed by a melt at 106 °C in the second and third scans of the same sample. Adding the succinic acid "spacer" increases the peak melting point of a bio-olefin, an observation evident through comparison of polymer **33** (Figure 4-6) with the other lysine branched polymers **31** (Figure 4-5) and **40** (Figure 4-10), which have the amino acid directly attached to the backbone and melt (T_m) 27 °C and 10 °C lower, respectively. It may be that the spacer provides additional freedom for the amino acid moiety to order.

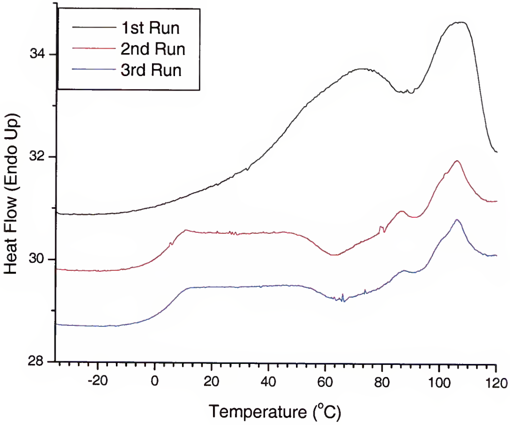


Figure 4-12. The DSC scans of polymer **33**, demonstrating cold crystallization phenomenon

Although both dipeptide branched polymers **34** and **35** crystallize and possess similar melting points, they appear to do so at different crystallization rates, with the alanine-alanine polymer (**35**) appearing to be the slower of the two. In fact the semicrystalline form of polymer **35** can be generated only by casting from solution, whereas polymer **34** recrystallized from the melt. Similar responses were observed for the "*N*-terminus" polymer, **27**, and several of the "*C*-terminus" polymers as well. At this point we are unable to offer full explanations for the thermal behavior that is observed;

the x-ray scattering experiments are currently underway and the initial results are discussed in the next section.

Initial X-Ray Scattering Data

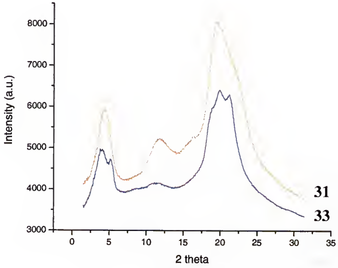


Figure 4-13. The WAXD patterns for the lysine branched polymers **31** and **33**.

As a follow-up to the research performed on the "*C*-terminus" polymers discussed in CH. 3, Dr. Kimberly Chaffin and Professor Frank Bates have analyzed the semicrystallinity observed for the lysine branched polymers **31** and **33** by WAXD and SAXD scattering. Polymer **33** differs from polymer **31** by the addition of a succinic acid spacer. A comparison of the WAXD patterns shows that the succinic acid spacer linkage causes two shoulders that are not observed for polymer **31** (Figure 4-13), and neither sample demonstrates long range ordering by the lack of a signal in the SAXD patterns (Figure 4-14). Both **31** and **33** seem to have the same general WAXD patterns as were observed for the "*C*-terminus" bio-olefins discussed in CH. 3, which suggests that the cause of crystallinity may be the same for all of the monomers. Indeed, it is possible that the amino acid/peptides are responsible for the semicrystallinity and not the polyolefin backbone.

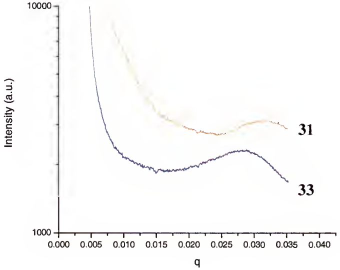


Figure 4-14. The SAXD patterns for the lysine branched polymers **31** and **33**.

Initial Instron Testing Data

In the pursuit of mechanical property testing, some initial Instron data has been collected with the help of our collaborators Mr. Clay Bohn and Professor Anthony Brennon. The data was collected by analyzing a dogbone sample that was cut out of a solvent-cast film (Figure 4-11) using a 500 g load cell. The thin films averaged a thickness of 0.19 mm. Two of the amorphous samples were analyzed as shown in Figure 4-15. Polymer **30**, which has a leucine methyl ester branch, was stretched 1.4 inches at which point the Instron stopped; the load cell was not heavy enough. This is an interesting phenomenon, and could be explained by hydrogen bonding interactions of the side chains. Further, upon sitting the polymer reformed its original dogbone shape. Polymer **29** was initially tested using an extensometer to analyze the sample (Figure 4-

16); however, the sample reached the instruments maximum elongation at 80 resulting in the instrument terminating the experiment — the sample was not broken. Similar to polymer **30**, the sample reformed the original dogbone shape with the distance between arrows (Figure 4-16) at 19 mm — only 1 mm from the original distance of 18 mm. The relationship shown in Figure 4-15 came from the 2nd analysis of polymer **30** using the same sample that had already been stretched. This time the measurement was performed using the crosshead distance to measure the extension rather than the extensometer. These results bring up a couple of interesting questions: are these amorphous bio-olefins shape-memory polymers and is this phenomenon an example of elasticity? These are questions that we hope to answer as this collaboration progresses.

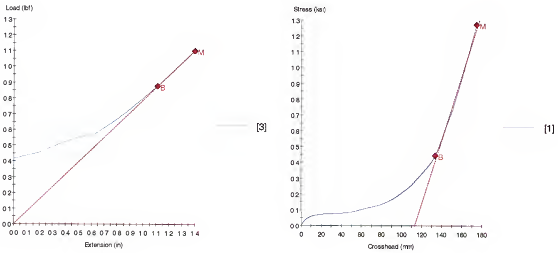


Figure 4-15. Instron data collected for polymers **30** (left) and **29** (right).

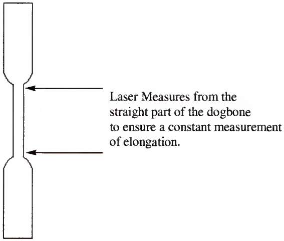

Laser Measures from the
straight part of the dogbone
to ensure a constant measurement
of elongation.

Figure 4-16. An illustration of the dogbones used for Instron testing showing the points at which the laser measures elongation.

Polymer **27** was also analyzed, but the instrument reached the maximum force almost immediately and terminated the experiment — the polymer never stretched. It appears the 500 g weight was not enough to pull the sample. One thing is clear from this initial work though: "*N*-terminus" bio-olefins, semicrystalline or amorphous, have good material properties, probably stemming from hydrogen bonding interactions.

Initial Surface Characterization

As discussed in CH. 3, the characterization of the polymer surface is essential to understanding the potential applications for these bio-olefins. For instance, having a cell-bindable unit such as RGD attached to a polymer backbone won't yield a biologically active polymer unless the peptide moieties are located on the polymer surface. Collaboration with Prof. Shunsaku Kimura and Mr. Shigekatsu Fujii at Kyoto University in Kyoto, Japan was started to answer the fundamental question: are the amino acid/peptide branches located on the surface?

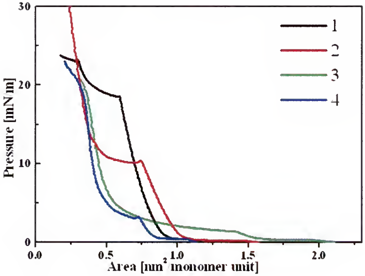
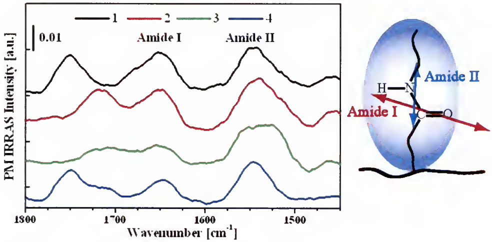


Figure 4-17. Surface pressure isotherm of dipeptide branched bio-olefins. Black is the alanine-alanine methyl ester branched polymer (34) and blue is the leucine-leucine methyl ester branched polymer (35). Also pictured red and green are "*C*-terminus" bio-olefins that were discussed in CH. 3.

The method employed was polarization modulation infrared reflective absorption spectroscopy (PM-IRRAS),[176-180] which was performed on a bio-olefin monolayer prepared in a Langmuir trough. Figure 4-17 shows the surface pressure isotherms of the bio-olefins **34** (black) and **35** (blue) taken during the monolayer film formation. The schematic in Figure 4-18 demonstrates the two amide stretches that were analyzed, where Amide I is the CO stretch and Amide II is the CN stretch. A ratio of the two IR signals gives the orientation of the peptide on the monolayer surface. As can be seen in Figure 4-19, the alanine-alanine branched polymer (**34**) is aligned at approximately 45° from the surface, whereas the bulky leucine-leucine branched polymer is located on the surface perpendicular to the backbone. This is in agreement with the data reported in the previous chapter, in which the more bulky peptides tend to be arranged at a 90° angle from the surface, probably due to steric reasons. Applying these findings to future goals, it would appear that the attachment of a biologically active peptide sequence to a bio-olefin should yield a polymer with the peptide moiety oriented in such a way as to maintain its biological activity.



Ratio of Amide I/Amide II
1: 0.88 4: 0.51

Figure 4-18. The PM-IRRAS spectrum of polymers **34** (black) and **35** (blue). Also pictured are the "*C*-terminus" bio-olefins (red and green) that were discussed in CH. 3.

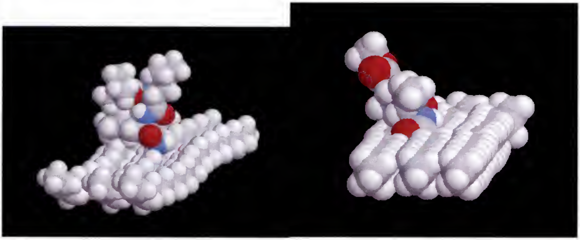


Figure 4-19. The 3-D representations of polymer **34** (left) and polymer **35** (right), demonstrating the configuration of the dipeptides on the surface of the polymer.

Work in Progress to Prepare a Biologically Active Bio-Olefin

Arginine-glycine-aspartic acid (RGD) is one of the shortest biologically active peptides.[194-195] Therefore, we were interested in producing a bio-olefin bearing this sequence to determine if the polyethylene backbone would affect the cell-binding ability of the peptide. As shown earlier, dipeptides polymerize easily, especially when attached to the diene through the *N*-terminus of the peptide; however, longer peptides had yet to be polymerized. Therefore, monomer **21** have an alanine-alanine-alanine methyl ester branch was synthesized (Figure 4-20).

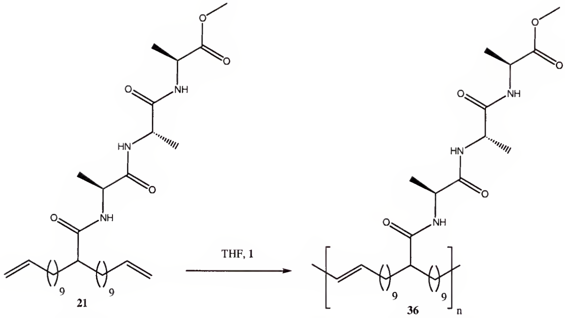


Figure 4-20. Polymerization of the alanine-alanine-alanine branched monomer **21** to polymer **36**.

The synthesis of monomer **21** was performed using the DIC/HOBt method described previously. However, the starting materials and the final product were insoluble in THF, so dimethylformamide (DMF) was added, which was a good solvent for the system. Alanine and poly(alanine) are known for a lack of solubility in common organic solvents. This lack of solubility caused another problem: what solvent will be suitable for polymerization? Unfortunately, many of the very polar solvents, such as DMF will deactivate the catalyst; therefore, an insoluble monomer to insoluble polymer polymerization was attempted (Figure 4-20). As mentioned previously, several polymerizations yielded a THF-insoluble product, yet the reaction still yielded high polymer. To our delight the polymerization appears to be a success. Characterization of this polymer is very difficult due to the lack of solubility in practically all common solvents. A small amount of polymer was dissolved in DMSO-d_6, and ^{1}H NMR appeared to demonstrate conversion to high polymer by the presence of internal olefin resonances at 5.32 ppm and the lack of external olefins at 5.00 and 5.85 ppm (Figure 4-21) — the method was not very quantitative due to the large variation in size of the polymer peaks versus the solvent resonances leading to a noisy background. GPC versus polystyrene gave a $\overline{M_n}$ of 4,000 g/mol; however, due to the insolubility of the polymer, most of the polymer sample (possibly higher molecular weight) was filtered out of the solution prior to injection of the GPC. So, it appears high polymer was formed from this insoluble monomer, which could prove to be an important observation, since many peptides lack solubility in common organic solvents such as THF.

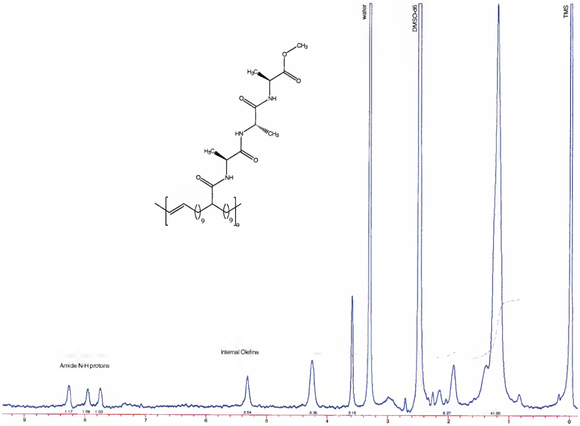
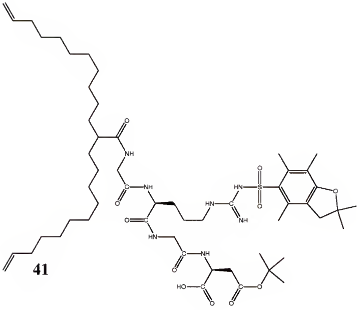


Figure 4-21. The ^{1}H NMR spectrum of polymer **36** demonstrating successful polymerization.

Since the methodology for the polymerization of longer peptides has been determined, the next step towards the synthesis of RGD-based bio-olefins was monomer preparation. The biological activity of RGD is strongly dependent on its secondary structure; thus, to help ensure the peptide would not be hindered by the backbone, a glycine unit was added between the backbone and the RGD sequence (Figure 4-22). Monomer synthesis was achieved using the Fmoc (*N*-(9-fluorenylmethoxycarbonyl) solid phase peptide synthetic strategy.[196] This methodology was chosen, since Fmoc is removed with piperidine (a weak base) allowing the side groups of arginine and aspartic acid to remain protected with PBf (2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl) and t-butyl (Figure 4-22). Further, it is essential that the side groups of the monomer remain protected to ensure catalyst longevity during metathesis. Solid phase peptide synthesis requires the use of a resin, usually polystyrene-based, that will allow for the proper amino acid arrangement, *N* or *C*-terminus, and cleavage under conditions that will not remove the protecting groups. In our case, since the peptide moiety will be attached to the diene through the *N*-terminus, it was necessary to use a resin that would attach to the *C*-terminus of the amino acid. The resin chosen for this work was 2-chlorotrityl chloride (Figure 4-23), since the peptide can be cleaved using a dilute trifluoroacetic acid or 2,2,2-trifluoroethane solution — at temperatures and concentrations low enough not to remove the t-butyl and Pbf protecting groups.



41

Figure 4-22. The GRGD-branched monomer **41**.

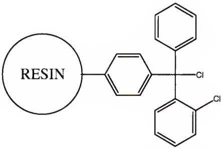


Figure 4-23. The 2-chlorotrityl chloride resin used in the synthesis of the GRGD monomer.

The synthesis was performed with the help of Mr. Chip Breitenkamp and Professor Todd Emrick in their laboratory at the University of Massachusetts. The procedure used was that of Chan and White.[196] The resins were first washed with CH_2Cl_2 using the apparatus shown in Figure 4-24, with a nitrogen purge to mix the resin and solvent, followed by the attachment of aspartic acid (1 mmol/g of resin) in *N,N*-diisopropylethylamine and CH_2Cl_2. By washing with DMF, CH_3OH, and (DIPEA), the excess reagents were removed and the free resin sites were blocked with methanol. The protecting groups were removed with piperidine, and the rest of the synthesis was performed using a Labmate solid phase peptide synthesizer (Figure 4-25). The Labmate is equipped with up to 24 individual reaction vessels, in which 1 gram of resin was placed in each container. For each coupling step, 5 equivalents of *O*-benotriazole-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium hexagluorophosphate (HBTU), amino acid, and HOBt were added and mixed for 30 minutes. Washing with DMF and deprotection with piperidine and washing with DMF again yielded the desired product ready for attachment of the next amino acid.

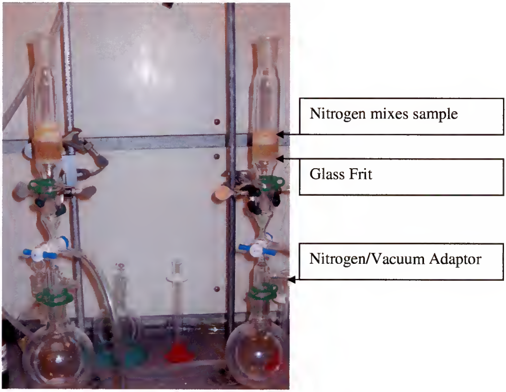


Figure 4-24. Apparatus used for washing the resin and attaching glycine to the resin.

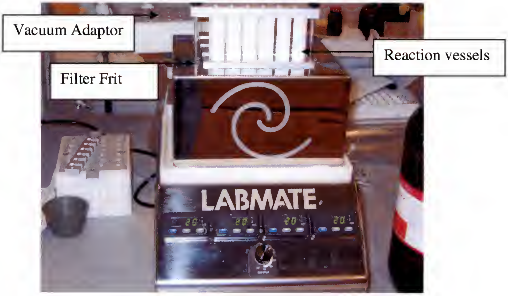


Figure 4-25. Solid-phase peptide synthesizer.

Due to the resin chosen, the diene could also be added via solid phase synthesis. However, a lack of solubility of the activated ester form of premonomer **4** in DMF may have hindered the reaction. Cleavage of the resin was accomplished using 2,2,2-trifluoroethanol, but isolation of the pure peptide proved difficult. The sample was recrystallized from ether/hexanes, but the monomers high solubility led to a low recovery of product. After analysis by HPLC/M.S., the monomer appears to be at least 50 % pure. At this point no further purification has been attempted, but TLC analysis suggests that multiple flash column chromatographies should isolate the product. Once the compound is purified and structure is verified by HRMS, ADMET will be attempted, and if successful, the polymer will be sent to Professor Sinskey at M.I.T. for cell binding studies.

Conclusions

Bio-olefins have been prepared using ADMET chemistry to give high molecular weight materials having melting points of up to 132 °C and 74 °C for amino acid and dipeptide branched polymers, respectively. Monomers with amino acids/peptides attached through the *N*-terminus of the amino acid polymerize more readily than monomers with amino acids/peptides attached through the *C*-terminus. For instance polymers with an amino acid branch on every 9th carbon polymerize nicely when attached through the *N*-terminus with catalyst **1**, but don't polymerize with the same catalyst when attached through the *C*-terminus.

The thermal data supports our previous suggestion[188,189] that the amino acid moiety and not the polymer backbone is responsible for the semicrystalline nature of the polymer, with the more polar amino acids tending to be semicrystalline (lysine) and the nonpolar amino acids (leucine) being amorphous, when located on every 21st Carbon. However, opposite results were observed when the branch is on every 9th carbon; only the leucine methyl ester branched polymers were semicrystalline not the lysine branched polymers. In addition, results for the arginine branched polymer **32** and dipeptide branched polymers **34** and **35** are encouraging when contemplating the polymerization of ADMET monomers possessing biologically active peptides such as the RGD sequence.

These bio-olefins described in this chapter have properties uncharacteristic of typical branched polyolefins, leading to many questions regarding structure property relationships. Initial data was reported demonstrating good material properties, *e.g.* elasticity and tensile strength. Further, over half of the bio-olefins are semicrystalline with up to 60 % crystallinity. In an attempt to investigate the surface of these bio-olefins, a monolayer was prepared via Langmuir trough, and investigated using PM-IRRAS. Preliminary examination of the dipeptide branched bio-olefins suggests that the more bulky the side chains the more perpendicular the branch is relative to the polymer surface.

The first tripeptide branched bio-olefin has been prepared by ADMET. Further, this polymerization occurred in a "semi-solid" state (the monomer/polymer were insoluble in the solvent), which could prove important since many peptides are insoluble in THF. The success of this reaction made the pursuit of the RGD based monomer feasible. This was accomplished by using a solid phase peptide synthesizer at the University of Massachusetts. The monomer was characterized by HPLC/MS, but has yet to be further purified from the initial workup.

Dissertation Overview and Future Perspective

Branched and linear bio-olefins have been prepared. These materials demonstrate film-forming capabilities, high crystallinity, elasticity and/or high tensile strength, and a surface functionalized with amino acid/peptide moieties. These properties could make ADMET bio-olefins useful as biocompatible materials for coatings, chiral separation media, biodegradable materials, drug delivery, etc.

Future work could be envisioned to incorporate both the linear and branched amino acids into one monomer. Amino acids, with side chain groups having amine or acid functionality, could be placed in the linear portion of the diene, and then amino acids/peptides could be attached to the side chain. The resulting linear-branched hybrid polymer should be semicrystalline and biodegradable; the polymer would be perfect for a new controlled-release drug delivery system. Further, incorporation of a cysteine moiety could allow for a crosslinkable site, and the resulting polymer could be used as a biodegradable hydrogel system, which should also have good drug delivery capabilities.

The branched bio-olefins discussed herein all have a polyethylene backbone. Therefore, future work should investigate the incorporation of ethers into the polymer backbone in an effort to make water soluble polymers. This could be accomplished via monomer synthesis, or by simple copolymerizations.

These are only a couple of the future prospects for this research. In addition to the modifications mentioned above, the incorporation of carbohydrates, nucleosides, and other biological entities are of interest, as well as longer peptide sequences. Several important questions still need to be answered: what is the limit for ADMET bio-olefins as far as peptide length, types of functionality, etc.? Further, any of the bio-olefins described herein could be deprotected and used as a substrate to react with longer peptides, and although the functionality won't be completely substituted, it should not matter in terms of biological applications. Finally, the extension of this project seems almost limitless at this point. It is an exciting area, and I am excited to see where and in what direction this research continues.

APPENDIX
WAXD AND SAXD DATA

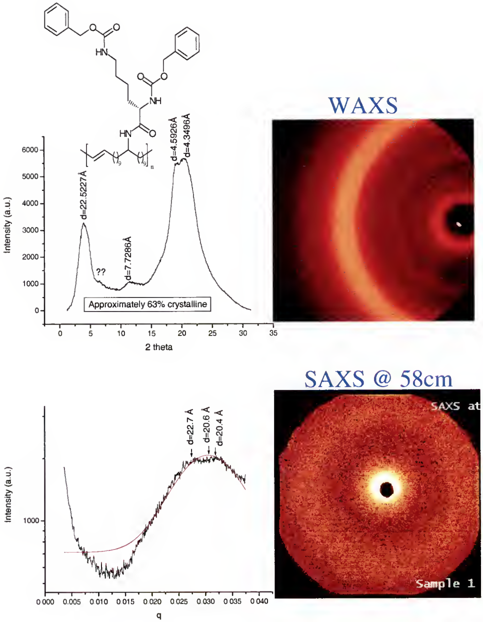


Figure A-1. WAXS and SAXS patterns for the 9-spacer di-CBz-lysine branched polymer.

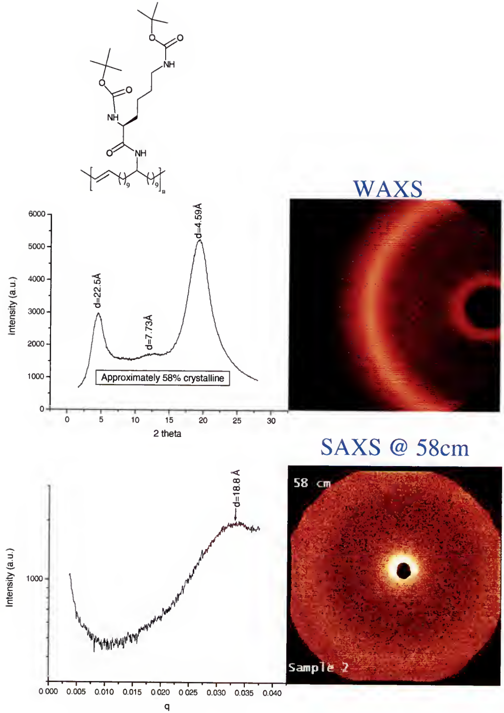
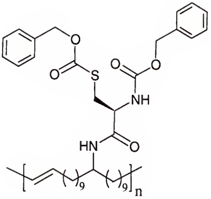
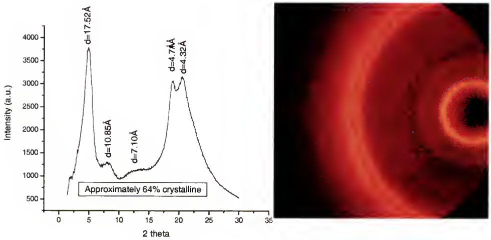


Figure A-2. WAXS and SAXS patterns for the 9-spacer di-BOC-lysine branched polymer.



WAXS



SAXS @ 58cm

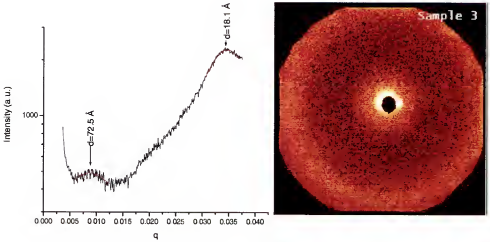


Figure A-3. WAXS and SAXS patterns for the 9-spacer di-CBz-cysteine branched polymer.

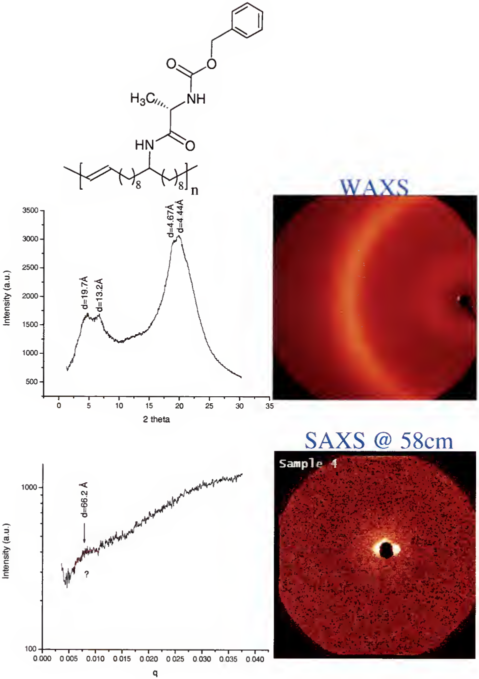


Figure A-4. WAXS and SAXS patterns for the 8-spacer CBz-alanine branched polymer.

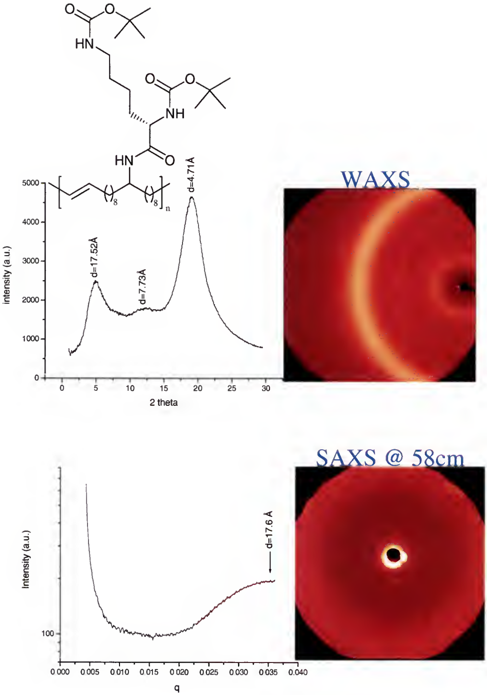


Figure A-5. WAXS and SAXS patterns for the 8-spacer di-BOC-Lysine branched polymer.

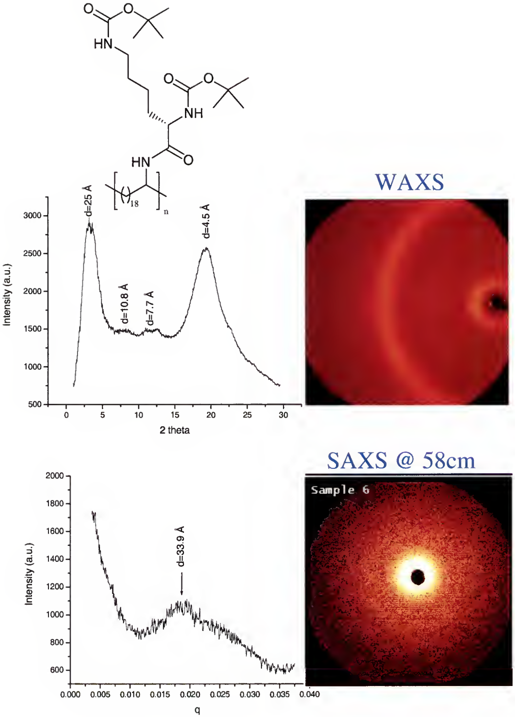


Figure A-6. WAXS and SAXS patterns for the hydrogenated 8-spacer di-BOC-Lysine branched polymer.

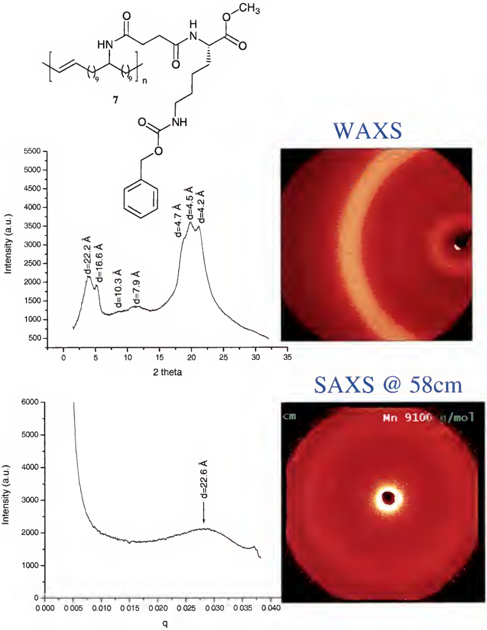


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Figure A-7. WAXS and SAXS patterns for the 9-spacer-Lysine(CBz)OCH_3 branched polymer with a succinic acid spacer between the backbone and the amino acid.

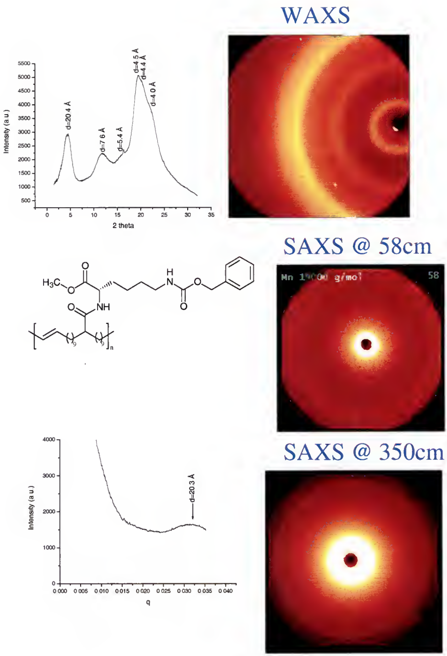

Figure A-8. WAXS and SAXS patterns for the 9-spacer-Lysine(CBz)OCH$_3$ branched polymer.

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BIOGRAPHICAL SKETCH

Timothy Edward Hopkins, son of Patricia and Edward Hopkins, was born in Springfield, Illinois on September 28, 1975. He lived in Sherman, Illinois throughout his youth, and attended Williamsville High School. While attending high school, he realized a love for sports, especially football. He graduated in May 1993.

After high school he continued his education at Blackburn College (a small, Work Program School — everything was student run). While at Blackburn College, he used their NCAA Division III status to extend his football career to the college level. After a couple of season-ending injuries, he remained involved with the team through assistant coaching. This was a valuable experience in learning to overcome the hardships of injury, and enhancing his leadership skills. Academically, he pursued a chemistry major with a math minor as part of a pre-engineering program with Washington University. However, chemistry became more and more enjoyable for him, and eventually became a greater interest than engineering. He graduated Summa Cum Laude with his B.A. in May 1997.

He spent the last two summers and winters of his undergraduate education working for the State of Illinois, Department of Transportation, Division of Materials and Physical Research as a chemist technician. Working in this environment motivated him to continue his education to obtain a more challenging work environment. This was accomplished by attending Southwest Missouri State University under the tutelage of Dr. Reza Herati. His masters research focused on the synthesis of new PEG-based drug-delivery systems; and most importantly, working at Southwest Missouri State University is where he discovered his love for research. He obtained his M.S. in chemistry in December 1999.

Following the path of another successful SMSU alumnus, Dennis Smith, he went to the University of Florida to work with Dr. Kenneth B. Wagener. While at the University of Florida, he was able to travel to Massachusetts Institute of Technology, the University of Massachusetts, New Orleans, Boston, and Orlando to tell the story of the development of the bio-olefin project in the Wagener Research Group. After a successful and enjoyable 4 years, he completed the requirements and received the degree of Doctor of Philosophy in December 2003.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth B Wagener

Kenneth B. Wagener, Chairman
George B. Butler Professor of Polymer Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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